FABRICATION AND EVALUATION OF DICLOFENAC SODIUM ENTERIC COATED PELLET DOSAGE FORM

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Under the Guidance of

Prof. K.G PARTHIBAN M.Pharm, Ph.D.

Head of Department

DEPARTMENT OF PHARMACEUTICS

J.K.K.MUNIRAJAH MEDICAL RESEARCH FOUNDATION

COLLEGE OF PHARMACY,

KOMARAPALAYAM-638183.

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ABBREVIATION

DS	Diclofenac sodium
OA	Osteo Arthritis
RA	Rheumatoid Arthritis
API	Active pharmaceutical ingredient
ACE	Angiotensin Converting enzyme
GI Tract	Gastro intestinal Tract
NSAID	Non steroidal anti inflammatory drugs
DMARD	Disease modifying anti-rheumatoid drug
FDA	Food and drug administration
NIR	Near infra red
FTIR	Fourier transform infrared
g	Gravity
MCC	Micro crystalline cellulose
PVP	Poly vinyl Pyrolidone
EC	Ethyl cellulose
UV	Ultra violet
PVA-PEG	Poly vinyl acetate – Poly ethylene glycol
TPI	Tera hertz pulsed imaging
HCL	Hydrochloride
hr	Hour
I.P	Indian pharmacopoeia
ICH	International conference on hormonization
Kg	Kilogram
SEM	Scanning Electron Microscopy

mg	Milli gram
mPas	Milli Pascal
mm	Millimeter
ml	Milliliter
RH	Relative humidity
SD	Standard deviation
Sec	Second
$t_{1/2}$	Half life
USP	United States of pharmacopoeia
PGET	Pellet gastric-emptying test
DCPA	Dexchlorpheniramine Maleate
Na - Ag	Sodium alginate
DSC	Differntial Scanning Calorimetry
IPA	Isopropyl alcohol
PEG	Poly ethylene glycol

SYMBOLS

±	Plus or minus
°	Degree
>	More than
<	Lesser than
µ	Micro
≡	Identical to
+	Plus
-	Minus
=	Equal to
/	Divide
%	Percentage
X	Multiply
[	Bracket open
]	Bracket close

1. INTRODUCTION

Despite the fact that significant advancements have been made in the development of well-designed systems to modify the oral delivery of drugs, the fundamental approaches have remained largely unchanged with the major systems being (a) insoluble matrix, (b) slowly eroding matrix, (c) swelling matrix, (d) polymer-coated tablets, (e) polymer coated pellets or granules, (f) osmotically driven systems, (g) systems controlled by ion exchange mechanisms, and (h) various combinations of these approaches. The scientific literatures are filled with new convoluted examples of oral modified-release systems, but the commercial applicability and success of many of these systems has to be realized.

Over the past 20 years, advances in oral modified-release technologies have been largely driven by substantial improvements in manufacturing equipment, most notably coating equipment, as well as the development of improved biocompatible and biodegradable polymeric materials for controlling release rates. A further driving force has been the development of a greater appreciation by both pharmaceutical scientists and regulatory authorities of the impact of physiological variability on the performance of modified-release products leading to more stringent requirements to ensure their safety and efficacy. The formulation of an enteric-coated product in the form of small individually enteric-coated granules or pellets (multi-particulates) contained in a rapidly dissolving hard gelatin capsule or a rapidly disintegrating tablet, largely eliminates the dependency of this type of dosage form on the all-or-nothing gastric emptying process associated with intact (monolith) enteric coated tablets. Provided the coated granules or pellets are sufficiently small (less than 1 mm diameter), they will be able to empty from the stomach with liquids. Hence enteric-coated granules and pellets exhibit a gradual but continual release from the stomach into the duodenum. This type of release also avoids the complete dose of drug being released into the duodenum, as occurs with an enteric-coated tablet. The intestinal mucosa is thus not exposed locally to a potentially toxic concentration of drug [(28)].

Historically, the term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of

manufacturing equipment. In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. The term also has been used to describe small rods with aspect ratios of close to unity. Although pellets have been used in the pharmaceutical industry for more than 4 decades, it has only been since the late 1970s, with the advent of controlled-release technology, that the advantages of pellets over single-unit dosage forms have been realized.

Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract. In addition pellets taken orally, disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs, and reduce inter and intra-patient variability.

Given the enormous advantages of multiparticulate systems over single-unit oral dosage forms, extensive research has focused recently on refining and optimizing existing pelletization techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment. The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusion–spheronization [(2)]

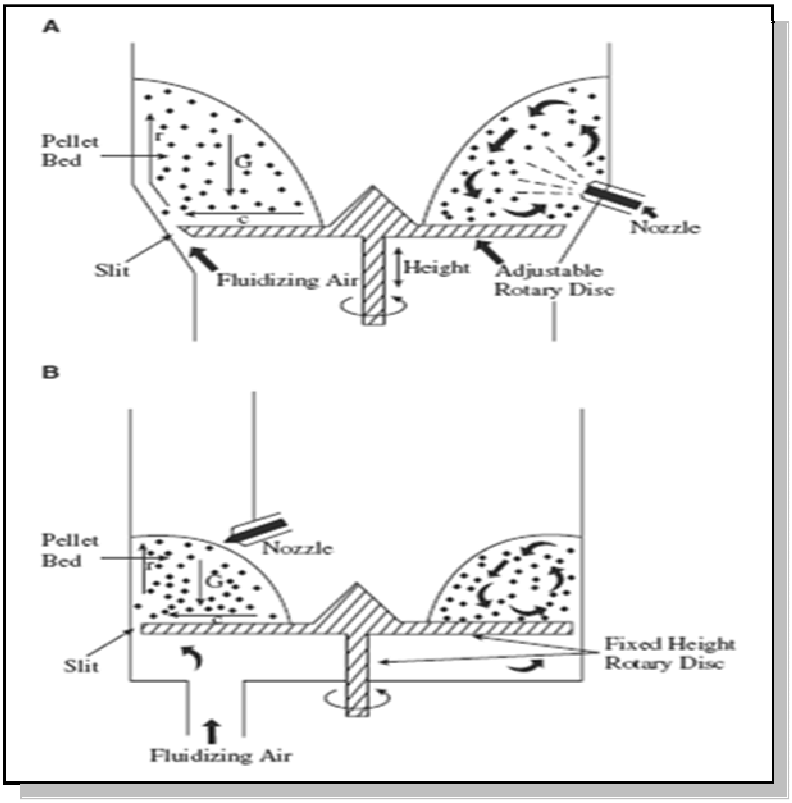
1.1 POWDER LAYERING

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on preformed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the binding liquid and dry powder, it generally requires specialized equipment.

The first equipment used to manufacture pellets on a commercial scale was the conventional coating pan, a machine that has been used by pharmaceutical firms, primarily for sugar coating, for a long time. Conventional coating pans, however, have had significant limitations as pelletization equipment. The degree of mixing is very poor,

and the drying process is not efficient. Mixing is a function of the pan shape, the tilt angle, the baffle arrangement, and the rotational speed of the pan itself. These parameters must be optimized to provide uniform drying and sufficient particle movement to eliminate the potential formation of dead spots during the operation and to maximize yield. For instance, during pelletization, elliptical pans tend to have fewer stagnant spots than do cylindrical pans and, consequently, are the equipment of choice. Reducing the tilt angle can also minimize formation of dead spots. If the rotational speed of the pan is too slow, segregation may occur owing to percolation and induce the preferential layering of drug onto larger particles. In addition, prolonged contact time among the particles could favor particle agglomeration if the liquid feed rate leads to surface wetness and stickiness that induce coalescence.

During powder layering, a binding solution and a finely milled powder are added simultaneously to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid. These liquid bridges are eventually replaced by solid bridges derived either from a binder in the application medium or from any material, including the drug substance, that is soluble in the liquid. Successive layering of the drug and binder solution continues until the desired pellet size is reached. Throughout the process, it is extremely important to deliver the powder accurately at a predetermined rate and in a manner that maintains equilibrium between the binder liquid application rate and the powder delivery rate. If the powder delivery rate is not maintained at predetermined equilibrium levels, over wetting or dust generation may occur, and neither the quality nor the yield of the product can be maximized. Toward the end of the layering process, it is likely that fines may be generated owing to potential interparticle and wall-to-particle friction and appears in the final product, thereby lowering the yield. The problem can be overcome if the application medium is sprayed on the cascading pellets at the end of the layering process to increase the moisture level at the pellet surface and facilitate layering of the fines onto the pellets. In an ideal process, no agglomeration occurs, and the particle population at the end of the process remains the same as that of the starter seeds or cores, with the only difference being an increase in the size of the pellets and thus in the total mass in the pan.



Fig, 1 Schematic representation of centrifugal fluid bed equipment and process with a single walled product chamber. A) Glatt GPCG and GRG Granulators and B) Freund CF Granulators.

Pieces of equipment that overcame the limitations of coating pans and revolutionized powder-layering processing as a pelletization technique are tangential spray or centrifugal fluid-bed granulators. Although tangential spray equipment was originally developed to perform granulation processes, its application was later expanded to cover other unit operations including the manufacture and coating of pellets.

Although there are variations in the design of centrifugal or rotary granulators, the basic operational principle that determines the degree of mixing and thus the efficiency of the process remains the same and includes centrifugal force, fluidization air velocity, and gravitational force **(Fig. 1).**During a layering process, these three forces act in concert to generate a spiral, rope-like motion of the particles in the product bed. The rotating disk, which may have fixed or variable speeds, creates a centrifugal force that pushes the particles outward to the vertical wall of the product chamber or stator. The fluidization

air, which is directed toward the slit between the periphery of the disk and the stator, generates a force that carries the particles vertically along the wall of the product container into the expansion chamber. The particles lose their momentum and cascade down toward the center of the rotating disk owing to gravitational force. The cycle repeats itself, bringing about a thorough mixing unparalleled by any other powder-layering equipment. The degree of mixing depends on the fluidization air volume and velocity, the slit width, the bed size, and the disk speed. These variables, as well as liquid and powder application rates, atomization air pressure, fluidization air temperature, and degree of moisture saturation determine the yield and quality of pellets.

1.2 SOLUTION / SUSPENSION LAYERING

Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. In principle, the factors that control coating processes apply to solution or suspension layering and, as a result, require basically the same processing equipment. Consequently, conventional coating pans, fluid bed centrifugal granulators, and Wurster coaters have been used successfully to manufacture pellets. The efficiency of the process and the quality of pellets produced are in part related to the type of equipment used.

The Wurster coating process, which was invented about 30 years ago, had evolved through elaborate design modifications and refinement into ideal equipment for the manufacture of pellets by solution/ suspension layering. The high drying efficiency inherent in fluid-bed equipment, coupled with the innovative and efficient design features of the Wurster process, has allowed the machines to hold center stage in pharmaceutical processing technology.

The primary features that distinguish Wurster equipment from other fluid-bed equipment are the cylindrical partition located in the product chamber and the configuration of the air distributor plate, also known as the orifice plate **(Figs. 2 and 3).** The latter is configured to allow most of the fluidization or drying air to pass at high velocity around the nozzle and through the partition, carrying with it the particles that are

being layered on. Once the particles exit the partition, they enter the expansion chamber, where the velocity of the air is reduced below the entrainment velocity, and the particles fall back to the area surrounding the partition (referred to as the down bed). The down bed is kept aerated by the small fraction of air that passes through the small holes on the periphery of the orifice plate.

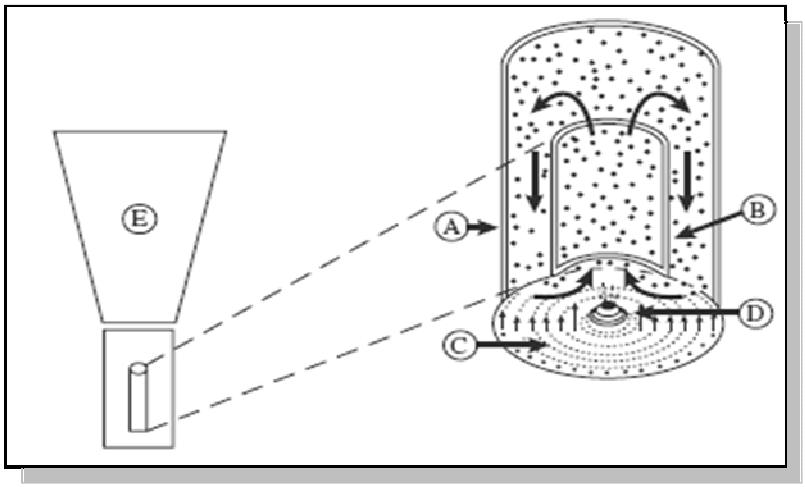


Fig. 2 Schematic representation of the Wurster product chamber and process. (A) Product Chamber, (B) Partition, (c) Orifice Plate, (D) Nozzle and E) Expansion Chamber.

The particles in the down bed are transported horizontally through the gap between the air distributor plate and the partition by suction generated by the high air velocity that prevails around the nozzle and immediately below the partition. The volume of air that passes through the down bed outside the partition is just enough to generate modest particle movement. Because the spray direction is concurrent with particle movement, and particle motion is well-organized under optimum conditions, uniform layering of drug substances is consistently achieved. Because the partition height, that is, the gap between the partition and the orifice plate, controls the rate at which the particles enter the spray zone, it is an important variable that needs to be optimized for every batch size.

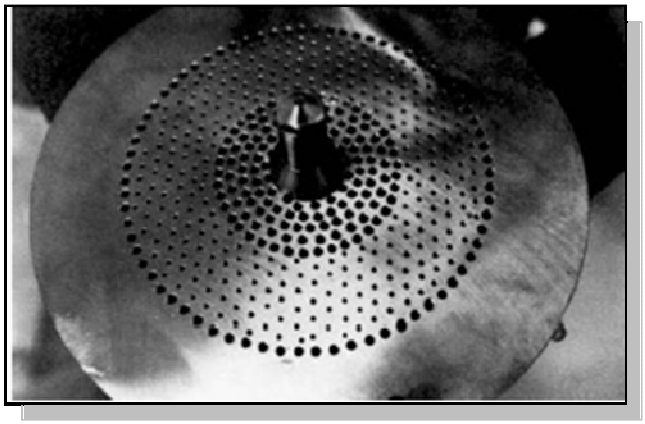


Fig. 3 Air Distributor or Orifice Plate of a Wurster Coater

The disadvantage of the Wurster process is the inaccessibility of the nozzles. If the nozzles are clogged at any time during the layering process, the operation has to be interrupted, and the spray guns must be removed for cleaning. The problem can be alleviated by screening the formulation or by using a spray gun with a bigger nozzle. Another aspect of the process that is challenging when multiple nozzles are used is the potential overlap of adjacent spray zones. Although the position of the nozzle is fixed, the spray zone overlap can be minimized using the air cap at the end of the spray gun.

Solution/suspension layering is usually used when the desired drug loading of the pellets is low because production of high-potency pellets from a low solids content formulation is not economically feasible. An important factor that needs to be considered when suspensions are used as opposed to solutions is the particle size of the drug. Micronized drug particles tend to provide pellets that are smooth in appearance, a property that is extremely desirable during subsequent film coating, particularly for controlled-release applications. If the particle size of the drug in the suspension is large, the amount of binder required to immobilize the particles onto the cores will be high, and, consequently, pellets of low potency are produced. The morphology of the finished pellets also tends to be rough and may adversely affect the coating process and the coated product. Moreover, because particles detach easily from the core they are being layered on owing to frictional forces, yield is usually low.

Although it is possible to manufacture pellets from a formulation that does not contain binders, almost invariably, the layers of drug applied tend to delaminate or break

off from the cores in the later stages of the layering process or in the subsequent drying step. Therefore, binders are consistently used during solution/suspension layering to impart strength to the pellets. They are usually low-molecular-weight polymers that are compatible with the drug substance.

They should not increase the viscosities of the formulations appreciably and should not, unless intended to do so, modify the release characteristics of the pellets.

1.3 EXTRUSION–SPHERONIZATION

For some applications it may be desirable to have a dense, spherical pellet of the type difficult to produce with the equipment above. Such pellets are used for controlled drug release products following coating with a suitable polymer coat and filling into hard gelatin capsules. Capsule filling with a mixture of coated and non-coated drug-containing pellets would give some degree of programmed drug release after the capsule shell dissolves. A commonly used process involves the separate processes of wet massing, followed by extrusion of this wet mass into rod-shaped granules and subsequent spheronization of these granules. Because this process is used so frequently to produce modified release multiparticulate.

Extrusion–spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening. The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, in which the powder is converted into a plastic mass that, can be easily extruded. The extruded strands are transferred into a spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and are pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally, owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved [(20)].

Extrusion–spheronization as a pelletization technique was developed in the early 1960s and since then has been researched and discussed extensively. The technology is unique in that it is not only suitable for the manufacture of pellets with a high drug loading but it also can be used to produce extended release pellets in certain situations in

a single step and thus can obviate the need for subsequent film coating. A variety of extruders, which differ in design features and operational principles, are currently on the market and can be classified as 1) Screw-Fed Extruders, 2) Gravity-Fed Extruders, and 3) Ram Extruders. Screw-fed extruders have screws that rotate along the horizontal axis and hence transport the material horizontally; they may be axial or radial screw extruders **(Fig. 4).** Axial extruders, which have a die plate that is positioned axially, consist of a feeding zone, a compression zone, and an extrusion zone. The product temperature is controlled during extrusion by jacketed barrels. In radial extruders, the transport zone is short, and the material is extruded radially through screens mounted around the horizontal axis of the screws. Gravity-fed extruders include the rotary cylinder and rotary gear extruders, which differ primarily in the design of the two counter-rotating cylinders **(Fig. 5).** In the rotary-cylinder extruder, one of the two counter-rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller. In the so-called rotary-gear extruder, there are two hollow counter-rotating gear cylinders with counter bored holes. In ram extruders, a piston displaces and forces the material through a die at the end **(Fig. 6).** Ram extruders are preferred during formulation development because they are designed to allow for measurement of the rheological properties of formulations. [9, 10, 11]

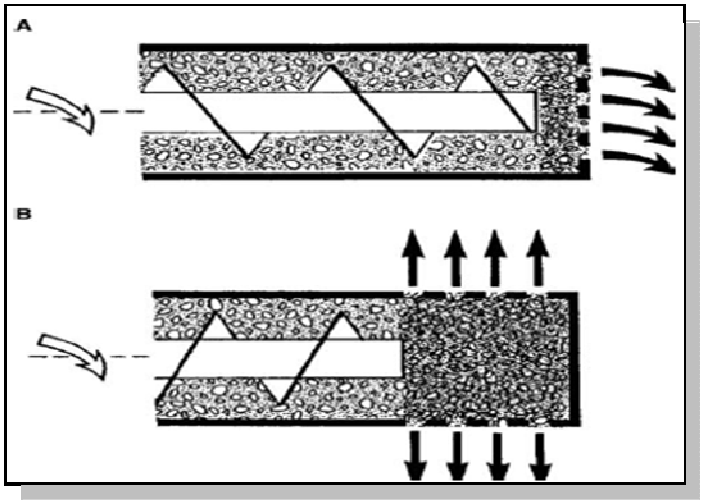


Fig. 4 Schematic representation of Screw Fed Extruders. (A) Axial Extruder and (B) Radial Extruder.

The extrusion/spheronization process was first introduced to the pharmaceutical industry in 1964 with the invention of the marumerizer. [13] Since then, significant improvements have been made to the machine, and currently well-designed marumerizers of different sizes are commercially available. A marumerizer or spheronizer consists of a static cylinder or stator and a rotating friction plate at the base. The stator can be jacketed for temperature control. The friction plate, which has a grooved surface, is the most critical part of the equipment that initiates the spheronization process. A typical friction plate has a crosshatch pattern, where the grooves intersect at a 90° angle, as shown in **(Fig. 7).** The groove width is selected based on the desired pellet diameter. Usually, groove diameters 1.5–2 times the target pellet diameter are used. The diameter of the friction plate is approximately 20 cm for laboratory scale equipment or up to 1.0m for production-scale units. The rotational speed of the friction plate is variable and ranges from 100 to 2000 rpm, depending on the diameter of the unit. A new variation of spheronizers that was introduced into the market is the so-called air-assisted spheronizers. Basically, they are similar to the standard spheronizers except that they are designed to permit a conditioned air stream to pass from beneath the rotating disk through the gap or slit between the cylindrical wall and the rotating friction plate into the product bed. The addition of such a feature presumably improves pellet turnover and brings about a spiral rope-like motion that facilitates spheronization. Axial-type extruders tend to produce extrudates with slightly higher densities. Twin-screw extruders have better material transport characteristics and higher capacity or throughput than do single screw extruders. Radial-type extruders have higher throughput but produce less dense extrudates than those obtained from axial-type extruders. The product temperature in radial extruders increases very little during the extrusion process, probably because of a shorter compression zone and shorter die opening depth. Absence of heat build-up during extrusion leads not only to well-controlled spheronization process but also allows for the processing of thermo labile drug substances. Although the extrusion step is a continuous process with a very high throughput, the subsequent steps (spheronization, drying, and sizing) are batch processes, and thus are rate limiting. As a result, the overall extrusion–spheronization process is a batch rather than a continuous process.

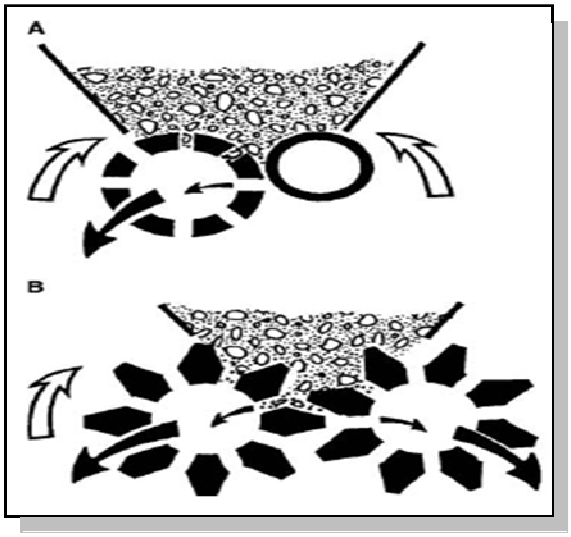


Fig. 5 Schematic representation of Gravity Fed Extruder. (A) Rotary Cylinder Extruder and (B) Rotary Gear Extruder.

Semi continuous process can be implemented by having an extruder feed, alternatively, into two spheronizers. As one of the spheronizers is spheronizing the extrudates, the other discharges the formed pellets and is recharged with fresh extrudates. The process is then repeated as the roles of the spheronizers are reversed alternately. In a batch process, a defined quantity of extrudate is fed into the spheronizer from the top, and the spheronized particles are discharged by centrifugal force via a discharge chute located at the base of the stator or vertical wall of the cylinder. The extrudates are spheronized by interparticle collisions and particle-to-wall frictional forces. The various stages of the spheronization process are shown in **(Fig. 8).** The spheronizing time is usually 2–15 min, depending on the formulation characteristics. Processing time remains constant, provided the composition of the extrudate, including the water content, and is kept constant. Because relatively large amounts of water or solvent are incorporated into the formulation, the final pellets contain significant quantities of residual moisture or solvent and are oven-dried or dried in a fluid-bed dryer before further processing. A sizing step might be necessary to separate the fractions if the particle size distribution is wider than intended. In general, the pellets are spherical and have a narrow particle size distribution.

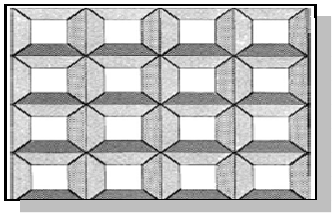


Fig. 6 Schematic representation of Ram Extruder.

The most critical process parameters in the spheronization step that influence the yield and quality are the design of the grooves and rotational speed of the friction plate and the residence time in the spheronizer. In an extrusion–spheronization process, formulation components such as fillers, lubricants, and pH modifiers play a critical role in producing pellets with the desired attributes. The granulated mass must be plastic and sufficiently cohesive and self-lubricating during extrusion. During the spheronization step, it is essential that the extrudates break at appropriate length and have sufficient surface moisture to enhance formation of uniform spherical pellets. The degree of liquid saturation of the granulation is another critical factor that needs to be optimized. Granulations containing low moisture content may generate extrudates that produce large quantities of fines during the spheronization step. If the moisture level is too high, the extrudates may adhere to each other and form bundles of strands that cannot be processed further. Therefore, the extrudates must have sufficient mechanical strength to form strands during the extrusion but must also be easily broken into uniform rods during spheronization to provide pellets with a narrow particle size distribution.

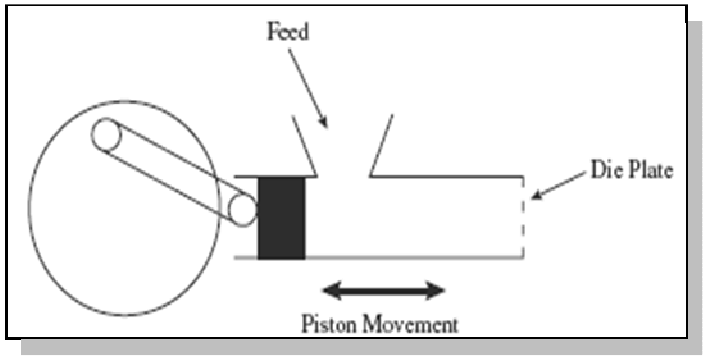


Fig. 7 Schematic representation of a spheronizer friction plate with a cross-hatch pattern

Excipients play a more significant role during extrusion–spheronization than during with any other pelletization process. They facilitate extrusion and determine the sphericity of the wet pellets; they also impart strength and integrity to the pellets.

In contrast to layering processes, extrusion– spheronization can be used to manufacture pellets with sustained-release characteristics without the application of functional membranes to control release.

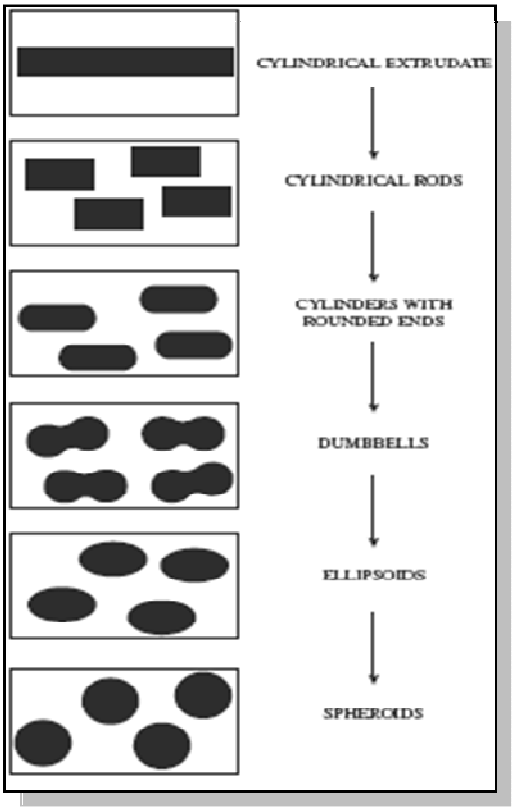


Fig. 8 Shape transitions during a spheronization process

Because extrusion–spheronization is a very complex manufacturing process that depends on a number of formulations and processing factors (Table 1), it has been studied extensively. Some of these studies used multifactorial statistical designs to determine the significance of the various factors. Despite the extensive work that had been done, additional research is still ongoing as demonstrated by the number of publications in various scientific journals.

1.4 SPHERICAL AGGLOMERATION

Spherical agglomeration, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action. Spherical agglomeration can be divided into two categories Liquid Induced and Melt Induced agglomerations. Over the years, spherical agglomeration has been carried out in horizontal drum pelletizers, inclined dish pelletizers, and tumbling blenders; more recent technologies use rotary fluid-bed granulators and high-shear mixers.

During liquid-induced agglomeration, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges. These are subsequently replaced by solid bridges, which are derived from the hardening binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets. The coalescence process continues until a condition arises in which bonding forces are overcome by breaking forces. At this point, coalescence is replaced by layering, whereby small particles adhere on much larger particles and increase the size of the latter until pelletization is completed. [30, 31]

If the surface moisture is not optimum, some particles may undergo nucleation and coalescence at different rates and form different sizes of nuclei admixed with the larger pellets. As a result, spherical agglomeration tends to produce pellets with a wide particle size distribution. The rate and extent of agglomerate formation depend, in part, on formulation variables such as particle size and solubility of the powder, the degree of liquid saturation, and the viscosity of the liquid phase.

Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges.

1.5 SPRAY DRYING AND SPRAY CONGEALING

Spray drying and spray congealing, known as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. The droplet size in both processes is kept small to maximize the rate of evaporation or congealing, and consequently the particle size of the pellets produced is usually very small. During spray drying, drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous.

During spray congealing, a drug substance is allowed to melt, disperse, or dissolve in hot melts of waxes, fatty acids, etc., and sprayed into an air chamber, where the temperature is below the melting temperatures of the formulation components, to provide spherical congealed pellets under appropriate processing conditions. A critical requirement in a spray congealing process is that the formulation components have well-defined, sharp melting points or narrow melting zones. Because the process does not involve evaporation of solvents, the pellets produced are dense and non-porous.

1.6 CRYOPELLETIZATION

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium. The technology, which was initially developed for lyophilization of viscous bacterial suspensions, can be used to produce drug-loaded pellets in liquid nitrogen at 160°C. The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The pellets are dried in conventional freeze dryers. The small size of the droplets and thus the large surface area facilitate the drying process. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and

temperature of the solution or suspension being processed. It is usually between 3 and 5 kg per kilogram of finished pellets.

The most critical step in cryopelletization is droplet formation, which is influenced not only by formulations-related variables such as viscosity, surface tension, and solids content but also by equipment design and the corresponding processing variables. The diameter and design of the shearing edge of the holes on the container plates are critical. Solutions or suspensions suitable for cryopelletization have high solids content and low viscosities. Another important property is the surface tension of the liquid formulation, which partly determines the pellet size. The addition of a surfactant to the formulation reduces the surface tension and results in smaller particle size. Pellet size also depends on the properties of the drug substance.

1.7 MELT SPHERONIZATION

Melt spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The process requires several pieces of equipment such as blenders, extruders, cutters (known as pelletizers in the plastics industry), and spheronizers. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature. The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter. The segments are spheronized in a jacketed spheronizer to generate uniformly sized pellets. The spheronization temperature needs to be high to partially soften the extrudate and facilitate deformation and eventual spheronization. [61] Depending on the characteristics of the formulation ingredients, pellets that exhibit immediate- or sustained release characteristics can be manufactured in a single step. The pellets produced are unique in that they are monosize, a property unmatched by any other pelletization technique. However, the process is still in the development stage, and additional work is needed before the process becomes a viable pelletization technique [(15)].

2.0 OSTEOARTHRITIS

Osteoarthritis (OA) is a common, slowly progressive disorder affecting primarily the weight-bearing diarthrodial joints of the peripheral and axial skeleton. It is characterized by progressive deterioration and loss of articular cartilage resulting in osteophyte formation, pain, limitation of motion, deformity, and progressive disability. Inflammation may or may not be present in the affected joints.

2.1 NONPHARMACOLOGIC THERAPY

- The first step is to educate the patient about the extent of the disease, prognosis, and management approach. Dietary counseling for overweight OA patients is warranted.

- Physical therapy with heat or cold treatments and an exercise programs helps to maintain and restore joint range of motion and reduce pain and muscle spasms. Exercise programs using isometric techniques are designed to strengthen muscles, improve joint function and motion, and decrease disability, pain, and the need for analgesic use.

- Assistive and orthotic devices such as canes, walkers, braces, heel cups, and insoles can be used during exercise or daily activities.

- Surgical procedures (e.g., osteotomy, joint debridement, osteophyte removal, partial or total arthroplasty, joint fusion) are indicated for patients with severe pain unresponsive to conservative therapy or pain that causes substantial functional disability and interference with lifestyle.

2.2 PHARMACOLOGIC THERAPY

2.2.1 General Approach

- Drug therapy in OA is targeted at relief of pain. Because OA often occurs in older individuals who have other medical conditions, a conservative approach to drug treatment is warranted.

- An individualized approach to treatment is necessary. For mild or moderate pain, topical analgesics or acetaminophen can be used. If these measures fail or if there

is inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful. Appropriate nondrug therapies should be continued when drug therapy is initiated.

2.2.2 Nonsteroidal Anti-Inflammatory Drugs

- NSAIDs at prescription strength are often prescribed for OA patients after treatment with acetaminophen proves ineffective, or for patients with inflammatory OA. Analgesic effects begin within 1 to 2 hours, whereas anti-inflammatory benefits may require 2 to 3 weeks of continuous therapy.

- All NSAIDs have similar efficacy in reducing pain and inflammation in OA (Table 1), although individual patient response differs among NSAIDs.

- Selection of an NSAID depends on prescriber experience, medication cost, patient preference, toxicities, and adherence issues. An individual patient should be given a trial of one drug that is adequate in time (2 to 3 weeks) and dose. If the first NSAID fails, another agent in the same or another chemical class can be tried; this process may be repeated until an effective drug is found. Combining two NSAIDs increases adverse effects without providing additional benefit.

- COX-2 selective inhibitors (e.g., celecoxib, valdecoxib) demonstrate analgesic benefits that are similar to traditional nonselective NSAIDs. Although COX-2 selective inhibition was designed to reduce NSAID-induced gastropathy (e.g., ulcers, bleeding, perforation), concerns about adverse cardiovascular events (e.g., myocardial infarction, stroke) have led authorities to recommend their use only in selected patients who are at high risk for NSAID-related gastrointestinal effects and low risk for cardiovascular toxicity.

- Gastrointestinal complaints are the most common adverse effects of NSAIDs. Minor complaints such as nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea occur in 10% to 60% of patients. NSAIDs should be taken with food or milk; except for enteric-coated products (milk or antacids may destroy the enteric coating and cause increased GI symptoms in some patients).

- All NSAIDs have the potential to cause gastric and duodenal ulcers and bleeding through direct (topical) or indirect (systemic) mechanisms. Risk factors for NSAID-associated ulcers and ulcer complications (perforation, gastric outlet obstruction, GI bleeding) include age more than 65 years, comorbid medical conditions (e.g., cardiovascular disease), concomitant corticosteroid or anticoagulant therapy, and history of peptic ulcer disease or upper GI bleeding.

- For OA patients who need an NSAID but are at high risk for GI complications, the ACR recommendations include either a COX-2 selective inhibitor or a nonselective NSAID in combination with either a proton pump inhibitor or misoprostol.

  NSAIDs may also cause renal complications, hepatitis, hypersensitivity reactions, rash, and central nervous system complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus. All nonselective NSAIDs inhibit COX-1-dependent thromboxane Production in platelets, thereby increasing bleeding risk. NSAIDs should be avoided in late pregnancy because of the risk of premature closure of the ductus arteriosus.

  The most potentially serious drug interactions include the concomitant use of NSAIDs with lithium, warfarin, oral hypoglycemics, high-dose methotrexate, antihypertensive, angiotensin-converting enzyme (ACE) inhibitors, I² blockers, and diuretics.

TABLE 1: **Medications Commonly Used in the Treatment of Osteoarthritis**

MEDICATION	DOSAGE AND FREQUENCY	MAXIMUM DOSAGE (MG/DAY)	
Oral analgesics			
Acetaminophen	325-650 mg every 4-6 h or 1 g 3-4 times/day	4000	
Tramadol	50-100 mg every 4-6 h	400	
Topical analgesics			
Capsaicin 0.025% or 0.075%	Apply to affected joint 3-4 times/day	-	
Nutritional supplements			
Glucosamine sulfate	500 mg 3 times/day or 1500 mg once daily	1500	
Nonsteroidal anti-inflammatory drugs (NSAIDs)			
Carboxylic acids			
Acetylated salicylates			
Aspirin, plain, buffered, or enteric-coated	325-650 mg every 4-6 h for pain.	3600[a]	
Nonacetylated salicylates			
Salsalate	500-1000 mg 2-3 times/day	3000[a]	
Diflunisal	500- 1000 mg 2 times/day	1500	
Choline salicylate[b]	500-1000 mg 2-3 times/day	3000[a]	
Choline magnesium salicylate	500-1000 mg 2-3 times/day	3000[a]	
Acetic acids			
Etodolac	800-1200 mg/day in divided doses	1200	
Diclofenac	100-150 mg/day in divided doses	200	
Indomethacin	25 mg 2-3 times/day; 75 mg SR once daily	200; 150	
Ketorolac[c]	10 mg every 4-6 h	40	
Nabumetone[d]	500-1000 mg 1-2 times/day	2000	
Propionic acids			
Fenoprofen	300-600 mg 3-4 times/day	3200	
Flurbiprofen	200-300 mg/day in 2-4 divided doses	300	
Ibuprofen	1200-3200 mg/day in 3-4 divided doses	3200	
Ketoprofen	150-300 mg/day in 3-4 divided doses	300	
Naproxen	250-500 mg twice a day	1500	
Naproxen sodium	275-550 mg twice a day	1375	
Oxaprozin	600-1200 mg daily	1800	
Fenamates			
Meclofenamate	200-400 mg/day in 3-4 divided doses	400	
Mefenamic acid[e]	250 mg every 6 h	1000	
Oxicams			
Piroxicam	10-20 mg daily	20	
Meloxicam	7.5 mg daily	15	
Coxibs			
Celecoxib	100 mg twice daily or 200 mg daily	200	
Valdecoxib	10 mg daily	10	

[a]Monitor serum salicylate levels over 3-3.6 g/day. [b]Only available as a liquid; 870 mg salicylate/5 mL.Not approved for treatment of OA for more than 5 days.[d]Nonorganic acid but metabolite is an acetic acid.[e]Not approved for treatment of OA.

3.0 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic and usually progressive inflammatory disorder of unknown etiology characterized by polyarticular symmetric joint involvement and systemic manifestations.

3.1 DESIRED OUTCOME

- The ultimate goal of RA treatment is to induce a complete remission, although this is seldom achieved.
- The primary objectives are to reduce joint swelling, stiffness, and pain; preserve range of motion and joint function; improve quality of life; prevent systemic complications; and slow destructive joint changes.

3.2 NONPHARMACOLOGIC THERAPY

- Adequate rest, weight reduction if obese, occupational therapy, physical therapy, and use of assistive devices may improve symptoms and help maintain joint function.
- Patients with severe disease may benefit from surgical procedures such as tenosynovectomy, tendon repair, and joint replacements.

3.3 PHARMACOLOGIC THERAPY

3.3.1 General Approach

- A disease-modifying antirheumatic drug (DMARD) should generally be started within the first 3 months of symptom onset. DMARDs should be used in all patients except those with limited disease or those with class IV disease in whom little reversibility is expected. Early use of DMARDs results in a more favorable outcome and can reduce mortality.
- First-line DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. The order of agent selection is not clearly defined. Hydroxychloroquine or sulfasalazine may be used initially in mild disease, butmethotrexate is often chosen initially in more severe cases because of long-term data suggesting superior outcomes than other DMARDs and lower cost than

biologic agents. Leflunomide appears to have long-term efficacy similar to methotrexate.

- Biologic agents with disease-modifying activity include the anti-TNF agents (etanercept, infliximab, adalimumab) and the interleukin-1 receptor antagonist anakinra. Biologic agents are effective for patients who fail treatment with other DMARDs.

- DMARDs that are less frequently used include azathioprine, penicillamine, gold salts (including auranofin), minocycline, cyclosporine, and cyclophosphamide. These agents have either less efficacy or high toxicity, or both.

- Combination therapy with two or more DMARDs may be effective when single-DMARD treatment is unsuccessful. Combinations that are particularly effective include (1) methotrexate plus cyclosporine, and (2) methotrexate plus sulfasalazine and hydroxychloroquine.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids may be used for symptomatic relief if needed. They provide relatively rapid improvement compared with DMARDs, which may take weeks to months before benefit is seen. However, NSAIDs have no impact on disease progression, and corticosteroids have the potential for long-term complications.

- See Table 2 for usual dosages and monitoring parameters for DMARDs and NSAIDs used in rheumatoid arthritis.

3.3.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

NSAIDs act primarily by inhibiting prostaglandin synthesis, which is only a small portion of the inflammatory cascade. They possess both analgesic and anti-inflammatory properties and reduce stiffness but do not slow disease progression or prevent bony erosions or joint deformity. They should seldom be used as monotherapy for rheumatoid arthritis.

TABLE 2: **Clinical Monitoring Of Drug Therapy In Rheumatoid Arthritis**

DRUG	TOXICITIES REQUIRING MONITORING	SYMPTOMS TO INQUIRE ABOUT A
NSAIDs and salicylates	Gl ulceration and bleeding, renal damage	Blood in stool, black stool, dyspepsia, nausea/vomiting, weakness
Corticosteroids	Hypertension, hyperglycemia, osteoporosis[b]	Blood pressure if available, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain, headaches, broken bones or bone pain
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	Symptoms of myelosuppression (extreme fatigue, easy bleeding or bruising, infection), jaundice
Gold (intramuscular or oral)	Myelosuppression, proteinuria, rash, stomatitis	Symptoms of myelosuppression, edema, rash, oral ulcers, diarrhea
Hydroxychloroquine	Macular damage, rash, diarrhea	Visual changes including a decrease in night
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis, stomatitis, rash	Symptoms of myelosuppression, shortness of breath, nausea/vomiting lymph node swelling, coughing
Leflunomide	Hepatitis, Gl distress, alopecia	Nausea/vomiting, gastritis, diarrhea, hair loss, jaundice
Penicillamine	Myelosuppression, proteinuria, stomatitis, rash, dysgeusia	Symptoms of myelosuppression, edema, rash, diarrhea, altered taste
Sulfasalazine	Myelosuppression, rash	Symptoms of myelosuppression, photosensitivity, rash, nausea/vomiting
Etanercept, adalimumab, anakinra	Local injection-site reactions, infection	Symptoms of infection
Infliximab	Immune reactions, infection	Postinfusion reactions, symptoms of infection

[a] Altered immune function increases infection, which should be considered, particularly in patients taking azathioprine, methotrexate, corticosteroids, or other drugs that may produce myelosuppression. [b] Osteoporosis is not likely to manifest early in treatment, but all patients should be taking appropriate steps to prevent bone loss.

- Cyclooxygenase-2 (COX-2) selective NSAIDs have a better gastrointestinal (GI) safety profile and similar efficacy as conventional NSAIDs.

TABLE 3: **Dosage Regimens for Nonsteroidal Anti-Inflammatory Drugs**

Recommended Total Daily Anti-inflammatory Dosage			
Drug	**Adult**	**Children**	**Dosing Schedule**
Aspirin	2.6-5.2 g	60-100 mg/kg	4 times daily
Celecoxib	200-400 mg	-	Once or twice daily
Diclofenac	150-200 mg	-	3-4 times daily Extended release: twice daily
Diflunisal	0.5-1.5 g	-	Twice daily
Etodolac	0.2-1.2 g (max, 20 mg/kg)	-	3-4 times daily
Fenoprofen	0.9-3.0 g	-	4 times daily
Flurbiprofen	200-300 mg	-	2-4 times daily
Ibuprofen	1.2-3.2 g	20-40 mg/kg	3-4 times daily
Indomethacin	50-200 mg	2-4 mg/kg (max, 200 mg)	2-4 times daily Extended release: once daily
Ketoprofen	150-300 mg	-	3-4 times daily Extended release: once daily
Meclofenamate	200-400 mg	-	3-4 times daily
Meloxicam	7.5-15 mg	-	Once daily
Nabumetone	1-2 g	-	Once or twice daily
Naproxen	0.5-1.0 g	10 mg/kg	twice daily Extended release: once daily
Naproxen sodium	0.55-1.1 g	-	Twice daily
Nonacetylated salicylates	1.2-4.8 g		2-6 times daily
Oxaprozin	0.6-1.8 g (max, 26 mg/kg)		1-3 times daily
Piroxicam	10-20 mg	-	Once daily
Sulindac	300-400 mg	-	Twice daily
Tolmetin	0.6-1.8 g	15-30 mg/kg	3-4 times daily
Valdecoxib	10 mg	-	Once daily

Common NSAID dosage regimens are shown in Table 3.

2. LITERATURE REVIEW

Fu Jijun et al, (2011)[14] developed matrix extended release pellets of Diclofenac potassium using low amount of release modifying agents and compared its performance in vivo with coated pellets and matrix tablets. Coated pellets were prepared by extrusion spheronization, followed by double layer coating using different polymers separately. Bio availability study of different coated pellets revealed drug concentration in plasma of beagle dogs was too low to be detected.

J.C.O. Villanova et al, (2011)[59] evaluated the physicochemical and flow properties of new polymeric excipients of ethyl acrylate, methyl methacrylate and butyl methacrylate, synthesized by suspension polymerization using cellulose nanowhiskers as co-stabilizer, to be used as direct compression for modified release. Particle size analysis of the beads with cellulose nanowhiskers (CNWB) indicated that the presence of the nanowhiskers led to a reduction of particle size a. In vitro test showed that the nanowhiskers and beads produced are nontoxic. The beads are used to produce tablets by direct compression contained propranolol hydrochloride as model drug.

Claire Gendre et al, (2011)[6] Performed in-line Near Infrared (NIR) measurements inside a pan coater to monitor a coating operation in real-time, by predicting the increases in mass of coating materials and coating thickness. A polymer combination of ethyl cellulose/poly (vinyl-alcohol)–poly (ethylene-glycol) graft copolymer was used as functional aqueous coating. Coated tablets were sampled at regular interval during the coating operation, then subjected to both simple and fast weighing (n = 50) or accurate and non-destructive Terahertz Pulsed Imaging (TPI) measurements (n = 3).

Sonali R.Naikwade et al, (2009)[52] developed enteric coated pellets of piroxicam in order to avoid local gastrointestinal irritation which is major side effect of non steroidal anti inflammatory drugs. Pellets were made by extrusion–spheronization process .Three polymers namely Eudragit L100, cellulose acetate phthalate, and hydroxyl propyl methyl cellulose phthalate were used. Enteric pellets prepared using Eudragit L 100 gave promising results for matrix pellets.

Ekarat Jantratid et al,(2009)[11] developed *Invitro* dissolution of MR Diclofenac sodium pellets containing 100mg active ingredient was evaluated under simulated pre- and postprandial condition using USP Apparatus 3 (reciprocating cylinder, Bio-Dis) and 4 (flow-through cell) and results compared with compendial methods using USP Apparatus 1 (basket) and 2 (paddle). The *in vitro* results were compared with the *in vivo* data by means of Level A *in vitro–in vivo* correlation (IVIVC) and Weibull distribution analysis. The biorelevant dissolution tests predicted correctly that the release (and hence absorption) of Diclofenac sodium would be slower in the fed state than in the fasted state.

Youness Karrout et al, (2009)[62] prepared and characterized novel types of polymer coated pellets allowing for the site-specific delivery of drugs to the colon. 5-Aminosalicylic acid (5-ASA)-loaded beads were prepared by extrusion–spheronization and coated with different Nutriose: ethylcellulose blends. *In vitro* drug release from these systems was measured under exposure to fresh fecal samples from inflammatory bowel disease patients under anaerobic conditions.

Simon Ensslin et al, (2009)[50] clarified the influences of three coating parameters on the drug release from chlorpheniramine maleate pellets coated with blends of poly (vinyl acetate) (PVAc) and poly (vinyl alcohol)-poly (ethylene glycol) (PVA-PEG) polymer. The Solubilisation inside pellets was monitored by EPR spectroscopy. A mathematical model was developed and it offers possibility to achieve a defined drug release.

Tamara Iosio et al, (2008)[56] formulated pellets by extrusion /spheronization with two cohesive layers. One of them contains a self emulsifying system for vincopectine, a poorly water soluble model drug. Two layers were prepared: an inert layer of micro crystalline cellulose, lactose and water and second one wetted with self-emulsifying system. Pellets type II revealed improved drug solubility and in vivo bio availability.

Ahmed abdalla et al, (2008)[1] developed a new pellet based self-emulsifying (SE) drug delivery system for the oral delivery of poorly soluble drugs. Furthermore, investigated the influence of physiological dilution media and enzymatic digestion on the solublization capacity of the formulation for the model drug Progesterone. Lipid mixtures composed of Solutol® HS 15 and medium chain glycerides were optimized with respect

to their self-emulsifying properties. The liquid SE lipid was mixed with microcrystalline cellulose and transformed into pellets by extrusion/spheronization. The pellets were characterized for size, shape, surface characteristics and friability. Pellets with good properties (size, shape and friability) have been produced through the incorporation of a selected SE mixture into MCC.

Pornsak Sriamornsak et al, (2007)[18] investigated the possibility of producing alginate – based pellets by extrusion/spheronization .Two types of sodium alginate (30%) were evaluated in combination with theophylline (20%), micro crystalline cellulose (50%) and different granulation fluids. Most of pellet formulations released about 75-85%drug within 60 min and showed good fit to both Higuchi and Korsmeyer-Peppas equations.

Mauro Serratoni et al, (2007)[27] prepared pellets by extrusion /spheronization containing two model drugs (methyl and propyl parabens) of low water solubility. One type of pellets contained drugs mixed with lactose and micro crystalline cellulose and other types of pellets contained the model drugs dissolved in self -emulsifying system(4,8%)consisting of equal parts of mono glycerides and polysorbate 80 and MCC. The application of sub coating of hydroxypropyl methyl cellulose was able to reduce the release rate of methyl parabens self emulsifying ethyl cellulose coated pellets.

Caroline D´esir´ee Kablitz et al, (2006)[51] developed a highly efficient dry coating process to obtain an enteric film avoiding completely the use of organic solvents and water. Using hydroxypropyl methylcellulose acetate succinate (HPMCAS) an enteric coat should be obtained without adding talc as antitacking agent because of problems arising from microbiological contamination. Further on, a method was developed preparing isolated films in order to determine the glass transition temperature (*T*g) and the required process temperature. The dry coating process has been demonstrated to be a serious alternative to conventional solvent or water based coating processes.

Ross A. Kennedy et al, (2006)[46] Formulated Calcium alginate gel-coated pellets by forming an insoluble gel coat on extruded–spheronized pellets by interfacial complication. Alginate with high guluronic acid content gave the slowest release. The faster drug release in acidic media and 0.1M NaCl compared to water is probably due to

reduced calcium cross-linking in the gel. These results suggest that the pellet size, alginate type and concentration and dissolution medium influenced the swelling and drug release behavior of calcium alginate gel-coated pellets.

Els Mehuys et al, (2005)[12] developed an alternative technique for enteric coating consisting of the hot-melt extrusion of coating polymers. An enteric coating polymer (PVAP or HPMC AS), premixed with a plasticizer, was extruded into hollow cylinders. The hollow pipes were filled with a model drug and both open ends of the cylinders were closed, yielding hot-melt extruded enteric capsules. The enteric capsules showed excellent gastro-resistance, since no drug release was observed after 2 h 0.1N HCl. It can be concluded that hot-melt extruded capsules seem suitable as an alternative for enteric coating

Helton Santos et al, (2005)[19] investigated about compaction and compression of xanthan gum pellets and evaluated its drug release from tablets made of pellets. Formulation includes xanthan gum, at 16 %(w/w), Diclofenac sodium or ibuprofen, at 10 %(w/w) .An amount of 500mgof pellets fraction 1000-1400 µm were compacted in single punch press at maximum punch pressure of 125MPa using flat-faced punches. Tablets made of pellets comprising ibuprofen released model drug in bimodal fashion and release behavior was characterized as case II transport mechanism (release exponent of0.93).

Caroline De Brabander et al, (2004)[4] tested the bio-availability of ibuprofen from hot-melt extruded mini matrices based on ethyl cellulose and hydrophilic excipients. during the in vivo evaluation on oral dose of 300 mg was administered to healthy volunteers (n=9) in a randomized cross-over study and compared with a commercially available sustained release product(Ibu-slow).The plasma samples were analyzed by validated HPLC-UV method.

Ann Debunne et al, (2004)[3] investigated the influence of formulation and compression parameters on the properties of tablets, containing enteric-coated pellets, and on the integrity of the enteric polymer of the individual pellets after compression. Tablets consisted of enteric-coated pellets (containing 2.5% (w/w) piroxicam in combination with microcrystalline cellulose and sodium carboxymethyl cellulose (using Avicel® PH 101

and Avicel® CL 611 in a ratio of 1–3)), cushioning waxy pellets and 10% Kollidon® CL (as an external disintegrator). A dosing interval of 48 h prevented piroxicam accumulation following multiple dose administration.

H.Steckel et al, (2004)[54] prepared chitosan pellets using extrusion/ spheronization technology. Microcrystalline cellulose was used as additive in concentrations from 70 to 0%.The powder mixtures were extruded using demineralised water and diluted acetic acid in different powder to liquid ratios. With DM water as granulating fluid, pellets with a maximum of 50 %(m/m) could be produced.

A.Kramar et al, (2003)[23] evaluated three formulation parameters for the application of poly methacrylic films from aqueous dispersions in order to obtain multi particulate sustained release of Diclofenac sodium. The chosen independent variables, i.e., the concentration of plasticizer (tri ethyl citrate), methacrylate polymers ratio (Eudragit RS: Eudragit RL) and the quantity of coating dispersions were optimized with a three-factor Box-Behnken design. Different release profiles were obtained.

Hanan F.Kakish et al,(2002)[18] prepared modified –release dosage forms of diltiazem HCl and Diclofenac sodium .The development work comprised two main parts :(a) loading the drug into ethylene vinyl acetate (EVA)polymer ,and (b)generation of a non uniform concentration distribution of drug within the polymer matrix .Phase separation technique was successfully used to load diltiazem HCl and Diclofenac sodium into polymer at significant levels ,up to 81 and 76%respectively.

B.Sreenivasa Rao et al, (2002)[53] Studied the rifampicin release studies from ethyl cellulose coated non pareil beads. Propylene glycol and castor oil were used as plasticizers. The in vitro dissolution studies revealed that the release rate is inversely proportional to percent of coating thickness. It also depends on type of plasticizer used. The mechanism off drug release follows Higuchi diffusion model.

Sally Y. Choe et al, (2001)[47] validated the Pellet Gastric Emptying Test (PGET) as a marker of gastric emptying; a randomized, four-way crossover study was conducted with 12 healthy subjects. The study consisted of oral co-administration of enteric coated caffeine (CAFF) and acetaminophen (APAP) pellets in four treatment phases: Same Size

(100 kcal), Fasted, Small Liquid Meal (100 kcal), and Standard Meal (847 kcal). The time of first appearance of measurable drug marker in plasma, *initial,* was taken as the emptying time for the markers. The results suggest that the pellet gastric emptying test could prove useful in monitoring changes in transit times in the fasted and fed states and their impact on drug.

Karen M.O'Connor et al, (2001)[21] studied physiological properties of Diclofenac salts prepared using eight different counter ions and including five novel salts, obtained with the bases 2-amino-2-methyl-1, 3-propane diol, 2-amino -2-methyl propranolol, tert-butylamine, benzyl amine and deanol .Characterisation techniques included X-Ray diffraction, differential scanning calorimetry, thermo gravimetric analysis, thermo microscopy, karl fischer titration, FT-IR and elemental analysis. The solubility of Diclofenac deanol was higher than Diclofenac salts.

T. Waaler et al, (1999)[60] Formulated Enteric coated dexchlorpheniramine maleate (DCPA) tablets and pellets with varying coating thickness and subjected to several in vitro tests after irradiation by thermal neutrons in a flux of 1.1310 n cm s for 2, 4 or 15 min. The appearance of the tablet formulation changed extensively after exposure of the tablets to pile radiation. The irradiation caused the film to loosen from the surface of the core, indicating the generation of gases during the irradiation process. Although the dissolution behavior of the pellet formulations changed significantly after the irradiation procedure, the changes were too small to be attributed exclusively to radiation damage.

Anandrao R. Kulkarni et al, (1999)[2] formulated Controlled release sodium alginate _Na–Alg. beads containing Diclofenac sodium by precipitation of Na–Alg in alcohol followed by cross linking with glutaraldehyde in acidic medium. Preparation of the beads was optimized by considering the percentage entrapment efficiency, swelling capacity of beads in water and their release data. The beads produced at higher temperatures and longer times of exposure to the cross linking agent have shown the lower entrapment efficiency, but extended release of DS from the beads.

M. Marvola et al, (1999)[26] developed a multiple-unit, site-specific drug formulation allowing targeting of drug release in the colon. Ibuprofen and furosemide were used as

model drugs. The former is absorbed throughout the gastrointestinal tract, the latter only from upper parts. Methacrylate copolymers, hydroxypropyl methylcellulose acetate succinate and cellulose acetate phthalate were used as enteric polymers. The main conclusion was that drug release can be targeted on the distal part of the small intestine and the colon by preparing film-coated matrix pellets in which enteric polymers dissolving at pH 7 have been used both as binders in the pellets and as coating material.

C. Lustig-Gustafsson et al, (1999)[25] investigated the influence of drug solubility in the range 14.3–1000 g l on the formation of pellets by extrusion and spheronization by evaluating the performance of a series of model drugs mixed with an equal part by weight of microcrystalline cellulose. The optimum water level required to form the best quality pellets was found to decrease as a linear function of the natural logarithm of the water solubility of the drug.

M.J.Fernandez-Hervas et al, (1998)[13] formulated alginate beads containing Diclofenac hydroxyl ethylyrolidine with either Eudragit or chitosan in order to achieve enteric formulation .In all cases, high entrapment efficiencies were obtained. Under conditions mimicking those in stomach, a small amount of drug was released.

J.Vertommen et al, (1997)[58] studied the shape and surface smoothness of pellets made in rotary processor by wet granulation. Optical microscopy combined with image analysis was used to determine three shape parameters (circularity, roundness and elongation) and fractal dimension, which is a characteristic for surface smoothness of pellets. This study reveals that pellets made in rotary processor are more variable in terms of their shepricity than in terms of their elongation.

P.B.Deasy et al, (1997)[7] developed two new pelletized formulations of Indomethacin and compared against pellets from proprietary product, Indocid-R. Extensive dissolution testing showed new product containing polyvinyl pyrolidone had slightly faster in –vitro release than commercial product. The other new product containing sodium lauryl sulphate had reduced release rate.

Timm Trenktrog et al, (1996)[57] Formulated pellets with human insulin as model drug by extrusion-spheronization process to investigate oral application of peptides. The

developed formulation was completed by addition of aprotonin as protease inhibitor sodium cholate as an intestinal absorption enhancer to enhance bio-availability of insulin. Further coated with shellac to protect the peptide against gastric juice .rapid and complete release of molecular –dispersed insulin from pellets was found in simulated intestinal fluid (PH 7.5).

J.Sujja-areevath et al, (1996)[55] designed an oral sustained release multiple-unit dosage form of Diclofenac sodium and evaluated the use of four natural hydrophilic gums as mini -matrix formulations enclosed in hard gelatin capsule. Carrageenan, locust bean, karaya and xanthan gums were used to produce mini-matrices. The amount of gum present play dominant role in determining drug release rate.

M.P.Gouldson et al, (1996)[16] investigated for the in-situ formation of an enteric co – precipitate of nifidipine with hydroxypropyl methylcellulose phthalate (HP-55) in spherical pellets. The use of various spheronization aids such as lactose, kaolin, aerosol 972 and 200, Bentone 27, liquid paraffin and magnesium state was studied. The final product containing sodium lauryl sulphate 2%as wetting agent and starch glycolate 5% as disintegrant processed with optimum solvent level, gave high yield of acceptable spheres.

Klaus knop et al,(1996)[22] Used aqueous dispersions of acrylic resins poly ethyl acrylate-methyl methacrylate-tri methyl ammonio ethyl methacrylate chloride(Quaternary PMMA,Eudragit RS 30D) and poly ethyl acrylate-methyl methacrylate (Nuetral PMMA ,Eudragit NE 30D) to cast free films and to coat theophylline pellets. The release of theophylline from pellets coated with Eudragit RS showed a great dependence on composition of buffer solution. The highest release rates were observed in format buffers, intermediate in phosphate buffers, low in citrate buffers and in buffers containing chloride ions.

W.Gunder et al, (1995)[17] Designed diffusion pellets (coated pellets) by adding Hydroxyl propyl methyl cellulose to aqueous ethyl cellulose (EC) dispersions with 20% dibutyl Sebacate(DBS) as plasticizer. Formulated diffusion pellets contain water-filled pores in release-controlling membrane after extraction of HPMC at beginning of release process.

Drug is released practically exclusively via distribution-diffusion mechanism. Pores also close in case of HMPC content of 30-40% but not completely.

Delphine Blanque et al, (1995)[8] evaluated the influence of formulation factors such as drug solubility, drug content, the quantity and type of release modifying agents and type of filler on formation and drug release from pellets formed by extrusion /spheronization. The molecular weight of polyethylene glycols was shown to be main factor influencing median pellet size and steady state extrusion force. Important factors appeared to be drug solubility and choice of filler

Sanjay R.Goskonda et al, (1994)[48] developed modified-release spherical pellets using a radial basket-type extruder and serrated plate spheronizer. A Box-Behnken response surface experimental design was employed to address the effects of altering the concentration of Eudragit RS 30D,Avicel RC-591,Fumaric acid, and acetyl tri butyl citrate .Controlled release pellets were produced that met dissolution specifications without subsequent coating.

3. AIM AND OBJECTIVE

Aim of the present research study is to develop Diclofenac sodium enteric coated pellets using Kollicoat MAE 100 P and Eudragit L 100 by Extrusion-Marumerisation technique.

Objective Diclofenac sodium is a water insoluble non steroidal anti inflammatory drug used in the treatment of chronic rheumatoid arthritis and osteoarthritis. Diclofenac sodium was enteric coated and presented as enteric coated Diclofenac sodium pellet in a capsule dosage form.

The key target of our study is to fabricate a Diclofenac pellets with uniform size and shape which increases the gastrointestinal transit time. In order to protect Diclofenac sodium release in the stomach, pellets were enteric coated and made available in the small intestine for release in the range of 6 – 7.5pH.

Rationale for the selection of dosage form is to minimize large variation in gastric emptying / residence time, less susceptible to dose dumping, facilitate accurate delivery of small quantity of potent drugs, reduced drug concentration at sites other than target organ, and maximizes drug absorption in small intestine, reduced potential side effects without lowering drug bio availability.

Rationale for the selection of enteric coating Diclofenac sodium has been reported with GI bleeding, ulceration and perforation can be fatal. So, Diclofenac sodium was enteric coated with enteric coating polymer such as Kollicoat MAE 100P , Eudragit L 100 and minimized the release in the stomach.

4. PLAN AND SCOPE OF THE WORK

Objective of the study is to produce an enteric coated pellet dosage form using Diclofenac sodium. It is achieved by doing preformulation, formulation, evaluation, and stability studies for the drug and excipients.

A) Preformulation studies:

1) Active pharmaceutical ingredient profile study
2) Excipient profile study
3) Characterization of active pharmaceutical ingredient and polymer using FT-IR
4) Thermal analysis for characterizing interaction between drug and excipients
5) Analysis of excipients compatibility by stability studies.

B) Formulation and evaluation:

Fabrication of core pellets

1) Formulation of Diclofenac sodium pellets
2) Evaluation of Diclofenac sodium pellets

Enteric coating for core pellets

3) Enteric coating for optimized pellets with different enteric polymers
4) Evaluation of enteric coated pellets

Reproducibility for optimized batch

5) Reproducibility of core pellets and enteric coating with suitable polymer and its evaluations
6) SEM Analysis for core and coated pellets

C) Stability study of enteric coated pellets

D) Comparison with marketed sample

A) PREFORMULATION STUDIES:

Active pharmaceutical ingredient profile study[28]

Studying of API profile is essential and foremost stage in preformulation. The intrinsic reactivity of the APIs in the solid state is very important, because it can be accentuated by the presence of water. The reactivity of the drug is made possible through a four-step process:

- Molecular loosening or mobility.
- Molecular change: this involves breaking of chemical bonds of the reactant (drugs and/or excipients) and formation of the new one in the product.
- Solid solution formation.
- Separation of product.

Excipients profile study

Excipient profile study is based on the inherent properties of the excipients and their importance in the delivery of the active ingredients to the target site. Excipients are contradictory to their original statement as "inert," but they are "enabling" substances which change the character of a dosage form. This may react with API and affects the characteristics of drug and dosage form.

Characterization of active pharmaceutical ingredient and polymer using FT-IR[29]

Fourier transform infrared spectroscopy is a powerful tool for structural confirmation of the active drug, allowing the generation of much information with very little expenditure of drug substance or time. In this case, FT-IR required to aid in understanding the nature of the interactions and determines whether they are relevant in formulation development.

Thermal analysis for characterizing interaction between drugs and excipients[30]

Drug–excipients interaction is one of the most important considerations in solid dosage form development and in drug discovery programs. If this study done with inadequacy leads to serious consequences such as formation of new impurities, incomplete mass balance, destruction of the dosage form, unnecessary multiplicity of

prototype formulations, changes in physicochemical properties and inability to obtain successful dosage form.

Analysis of excipients compatibility using stability studies method

Excipient compatibility study done to find out the unwanted results on storage for a period of time, by this we may avoid spurious effects on developed dosage form on storage.

B) FORMULATION AND EVALUATION:

Formulation of Diclofenac sodium core pellets

Pellets were prepared by spheronization and marumarization method for the ease in preparation as well to require uniform size and shape to the pellets.

Evaluation of Diclofenac sodium core pellets

Angle of repose, bulk density, tapped density, Carr's index, Hauser's ratio, loss on drying water absorption ratio, friability, assay and dissolution are the parameters chosen to evaluate pellets.

Enteric coating for optimized core pellets

Enteric coating were done to the Diclofenac sodium pellets to minimize the release in the stomach and made available in the small intestine to reduce the unwanted side effects of the drug in the stomach.

Evaluation of enteric coated pellets

Angle of repose, bulk density, tapped density, Carr's index, Hauser's ratio, loss on drying water absorption ratio, friability, assay and *In-vitro* dissolution study was conducted for the enteric coated pellets to find the amount of Diclofenac sodium release in acidic pH.

Reproducibility for enteric coated pellets with its evaluation

Reproducibility of the optimized batch preparation was done with its respective core and coated pellets evaluations. These tests were done to pellets to find out its reproducibility on preparation and stability on administration, transportation and storage.

Scanning electron microscope for the core and coated pellets

SEM analysis was done to core and coated pellets to find out appropriate size of the pellets and to evident the increase in size of the pellets after coating.

C) STABILITY STUDY OF ENTERIC COATED PELLETS

In the development of enteric coated Diclofenac sodium pellets, the stability of the dosage form is evaluated; samples are stored under appropriate stressful environmental conditions so as to identify any circumstances that would lead to degradation of the dosage form. Examples of suitable stress would include increased temperature, elevated relative humidity, and exposure to high intensity light. Samples are withdrawn at definite time intervals and analyzed for the stability.

D) COMPARISON WITH MARKETED SAMPLE

The optimized pellet formulation (C8) was compared with marketed pellet formulation to find out the similarity and differences between them.

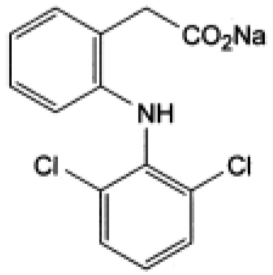
5. PREFORMULATION

5.1 ACTIVE PHARMACEUTICAL INGREDIENT PROFILE

5.1.1 Diclofenac sodium[10]

Therapeutic Category: Non steroidal anti-inflammatory drugs

Structure:



DICLOFENACSODIUM

Chemical Name: Sodium 2-[(2, 6-dichlorophenyl) amino] phenyl] acetate.

Molecular Formula: $C_{14}\ H_{10}Cl_2NNaO_2$

Molecular Weight: 318.1g/mol

Description: White or slightly yellowish, slightly hygroscopic, crystalline powder.

Appearance: White crystals

Solubility: Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96%) slightly soluble in acetone.

Melting point: About 280°C with decomposition.

Loss on drying: Maximum 0.5%, determined on 1.0g by drying in an oven at 105°C for 3h.

Residue on ignition: Not more than 0.1%

Heavy metals: Maximum 10ppm.

Dose: 75 to 150mg daily, in divided doses for adults.

Storage: in an air tight container protected from light.

Mechanism of Action:

The exact mechanism of action is not entirely known, but it is thought that the primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis. Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side-effect of diclofenac.

Pharmacokinetic profile:

Absorption: Diclofenac is completely absorbed after their passage through the stomach.

Distribution: 99.7% of Diclofenac is bound to serum proteins mainly to albumin (99.4%). Diclofenac enters the synovial fluid, where peak concentrations are measured 2.4 hrs after the peak plasma levels have been reached.

Half life: 1.0 – 2.0 hours

Metabolism: Biotransformation of Diclofenac takes place by glucuronidation partly of the intact molecule, but mainly by glucuronidation after single and multiple hydroxylations.

Excretion: 60% of the drug excreted via kidney as metabolites, less than 1.0% excreted unchanged in urine

Therapeutic uses: for the treatment of rheumatoid arthritis, osteoarthritis and as analgesic.

Contraindication: Peptic ulcer, known hypersensitivity reaction to the Diclofenac sodium. Like other non-steroidal anti-inflammatory agents, Diclofenac is contraindicated

in patients in whom attacks of asthma, urticaria or acute rhinitis have been precipitated by acetylsalicylic acid or other prostaglandin-synthetase inhibitors.

Adverse drug reactions

Gastrointestinal tract: Epigastric pain, other gastrointestinal symptoms, e.g., nausea, vomiting, diarrhea, abdominal cramps, dyspepsia, flatulence, anorexia, gastrointestinal bleeding, haematemesis, melaena, peptic ulcer with or without bleeding or perforation, bloody diarrhea, lower gut disorders leg. Non specific hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease); aphthous stomatitis, glossitis, oesophageal lesions, constipation.

Central (and peripheral) nervous system: Headache, dizziness or vertigo.

Skin: Skin rash, urticaria. **Kidney:** ***Isolated cases:*** Acute renal failure, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver: Elevated serum aminotransferases (SGOT, SGPT).

Hypersensitivity reactions: Hypersensitivity reactions, e.g. asthma, systemic anaphylactic / anaphylactoid reactions (including hypotension).

Drug interaction:

Lithium / digoxin: Diclofenac may raise plasma concentrations of lithium or digoxin when given together with preparations containing these substances.

Diuretics: Some nonsteroidal anti-inflammatory agents can inhibit the effect of diuretics. Concomitant treatment with potassium-sparing diuretics may raise serum potassium levels which should therefore be monitored.

NSAIDs: Concomitant administration of various systemic nonsteroidal anti-inflammatory drugs may increase the frequency of adverse effects.

Anticoagulants: Although no evidence appear to suggest that Diclofenac affects the action of anticoagulants, an increased risk of hemorrhage in patients receiving Diclofenac and anticoagulants concomitantly has been reported in isolated cases. It is therefore advisable to monitor such patients carefully.

Like other non steroidal ant rheumatic agents, Diclofenac may temporarily inhibit platelet aggregation when given in high doses (200 mg).

Ant diabetic agents: It has been shown that Diclofenac can be given concomitantly with oral ant diabetic agents without influencing their clinical effect.

However, isolated cases have been reported of hypoglycemic and hyperglycemic reactions, necessitating an adjustment in the dosage of anti diabetic drugs treatment with diclofenac.

Methotrexate: Caution is called for if nonsteroidal anti-inflammatory agents are administered < 24 hrs before or after treatment with methotrexate, since methotrexate levels in the blood may rise and the toxicity of this substance is increased.

Cyclosporine: The effect of non-steroidal anti-inflammatory drugs on renal prostaglandins may increase the nephrotoxicity of cyclosporine.

Dosage forms: Tablets, capsules as controlled release, drops and injection.

Marketed preparations:

Tablets: Dynapar, Diclomove, Inflamol, Valet, Udec, Fenbest.

Capsules: Regunac 100mg.

Drops: Icein, Diclolab, Diclol.

Injections: Diclonip, Diclostar, Antiflam, Dicoliv.

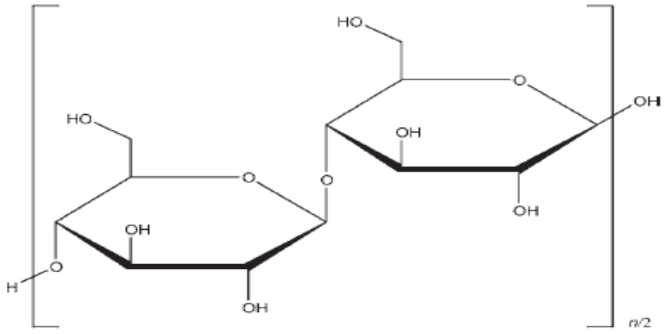
5.2 EXCIPIENTS PROFILE

5.2.1 Microcrystalline Cellulose[37]

Synonyms: Avicel PH; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; Emcocel; Ethispheres; Fibroce.

Chemical Name: Cellulose

Chemical structure:



Nonproprietary names:

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Description: Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

Melting point: Chars at 260 - 270°C

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications: Microcrystalline cellulose is used in pharmaceuticals, as a binder/diluent in oral tablet and capsule formulations.

Storage: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

TABLE NO 4: PROPERTIES OF COMMERCIALLY AVAILABLE GRADES OF MICROCRYSTALLINE CELLULOSE

Grade	Nominal mean particle size	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel pH 101	50	60 200	≤ 1.0 ≤ 30.0	≤ 5.0
Avicel pH 102	100	60 200	≤ 8.0 ≥ 45.0	≤ 5.0
Avicel pH 103	50	60 200	≤ 1.0 ≤ 30.0	≤ 3.0
Avicel pH 105	20	400	≤ 1.0	≤ 5.0
Avicel pH 112	100	60	≤ 8.0	≤ 1.5
Avicel pH 113	50	60 200	≤ 1.0 ≤ 30.0	≤ 1.5
Avicel pH 200	180	60 100	≥ 10.0 ≥ 50.0	≤ 5.0
Avicel pH 301	50	60 200	≤ 1.0 ≤ 30.0	≤ 5.0
Avicel pH 302	100	60 200	≤ 8.0 ≥ 45.0	≤ 5.0

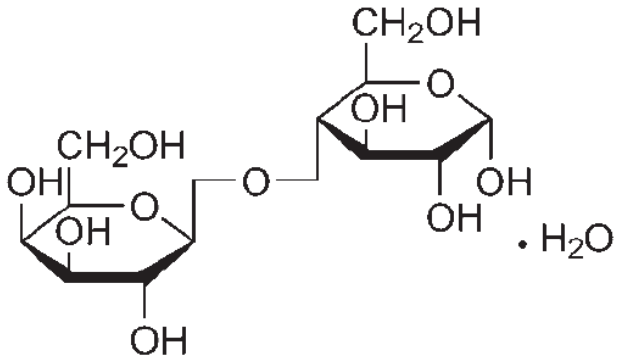
Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

5.2.2 Lactose Monohydrate[36]

Synonyms: Capsulac; Granulac; Lactochem; Lactosum Monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac, SorboLac, SpheroLac, SuperTab 30GR; Tablettose.

Chemical Name: O-β-D-Galactopyranosyl-b-D-glucopyranose monohydrate

Chemical structure:



α-Lactose monohydrate

Nonproprietary names:

BP: Lactose

JP: Lactose Hydrate

PhEur: Lactose Monohydrate

USP-NF: Lactose Monohydrate

Description: Lactose Monohydrate occurs as white to off-white crystalline particles or powder. **Melting point:** 201 - 202°C for dehydrated alpha lactose monohydrate

Solubility: Soluble in water; practically insoluble in ethanol, chloroform and ether.

Functional Category: Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluents; tablet and capsule filler.

Applications: Lactose is widely used in dry powders and direct compression tabletting applications, and as a tablet and capsule filler and binder.

Storage: Lactose should be stored in a well-closed container in a cool, dry place.

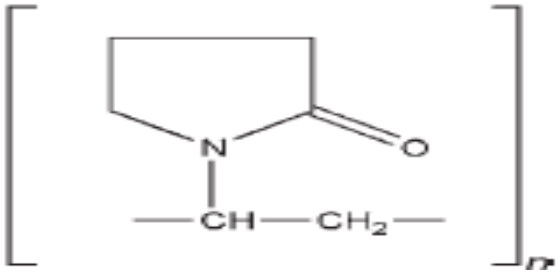
Incompatibilities: Lactose monohydrate is incompatible with primary, secondary amines, amino acids and amfetamines.

5.2.3 Povidone[40]

Synonyms: Kollidon; Plasdone; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

Chemical structure:



Nonproprietary names:

BP: Povidone

JP: Povidone

PhEur: Povidone

USP: Povidone

Description: Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Melting point: Softens at 1508C.

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Functional Category: Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Applications: In tabletting, povidone solutions are used as binders. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

Storage: Povidone is hygroscopic, should be stored in an airtight container in a cool, dry place.

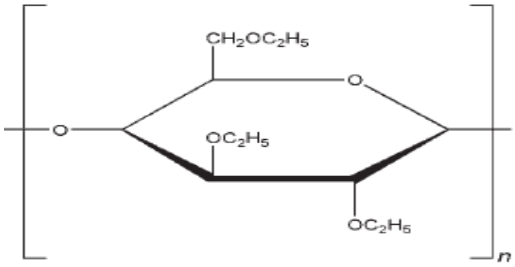
Incompatibilities: It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.

5.2.4 Ethyl Cellulose[34]

Synonyms: Aqua coat ECD; Aqualon; Ashacel; Ethocel; ethylcellulosum; Surelease.

Chemical Name: Cellulose ethyl ether

Chemical structure:



Nonproprietary names:

BP: Ethyl cellulose

PhEur: Ethyl cellulose

USP-NF: Ethyl cellulose

Description: It is a tasteless, free-flowing, and white to light tan-colored powder.

Specific gravity: 1.12–1.15 g/cm3

Solubility: Practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).

Functional Category: Coating agent; flavoring agent; tablet binder; viscosity increasing agent.

Applications: Ethyl cellulose is widely used as a hydrophobic coating agent for tablets and granules.

Storage: Ethyl cellulose is a stable, slightly hygroscopic material; it should be stored at a temperature not exceeding 328°C (908F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities: Incompatible with paraffin wax and microcrystalline wax.

5.2.5 Talc[43]

Synonyms: Altalc; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

Chemical Name: Octadecanoic acid magnesium salt

Nonproprietary names:

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Moisture content: Talc absorbs insignificant amounts of water at 258C and relative humidity up to about 90%.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Functional Category: Antitacking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications: Talc is also used as a lubricant in tablet formulations, adsorbent, dissolution retardant, and dusting powder.

Storage: Talc should be stored in a well-closed container in a cool, dry place.

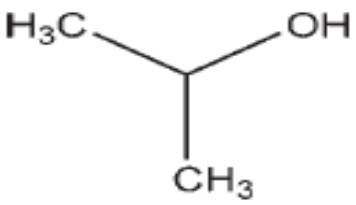
Incompatibilities: Incompatible with quaternary ammonium compounds.

5.2.6 Isopropyl alcohol[35]

Synonyms: Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol; rubbing alcohol.

Chemical Name: Propan-2-ol

Chemical structure:



Nonproprietary names:

BP: Isopropyl Alcohol

JP: Isopropanol

PhEur: Isopropyl Alcohol

USP: Isopropyl Alcohol

Description: Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone.

Melting point: 88.58°C

Solubility: Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

Functional Category: Disinfectant; and solvent.

Applications: Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, and topical disinfectant

Storage: Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

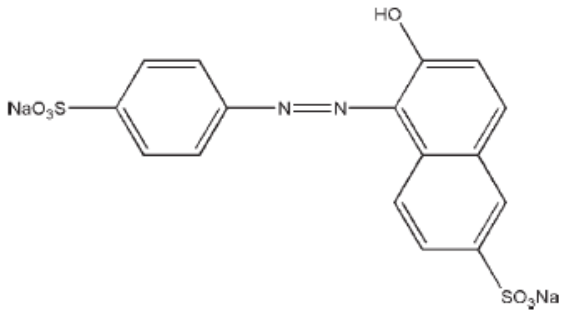
Incompatibilities: Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

5.2.7 Sunset Yellow[42]

Synonyms: FD&C yellow #6; yellow orange S.

Chemical Name: 6-hydroxy-5-[(4-sulfophenyl) azo]-2-naphthalenesulfonic acid disodium salt

Chemical structure:



Description: Reddish yellow powder. Aqueous solutions are bright orange colored.

Color Index No: CI 15985

Melting point: 300°C

Solubility: soluble in water in the ratio of 1 in 63 at 25°C less soluble in glycerin and ethanol(75%) partially insoluble in acetone.

Functional Category: Colouring agent.

Applications: Sunset yellow is often used in conjunction with E123, amaranth, in order to produce colouring in both chocolates and caramel.

Storage: It undergoes a phase change from an isotropic liquid to liquid crystal at room temperature. Store it in air tight light resistant container, cool, dry place.

Incompatibilities: Poorly compatible with citric acid, saccharose solutions, and saturated sodium bicarbonate solutions. Incompatible with ascorbic acid, gelatin, and glucose.

5.2.8 Polyethylene Glycol [38]

Synonyms: Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG

Chemical Name: a-Hydro-o-hydroxypoly (oxy-1, 2-ethanediyl)

Nonproprietary names:

BP: Macrogols

JP: Macrogol 400

Macrogol 4000

Macrogol 6000

PhEur: Macrogols

USP-NF: Polyethylene Glycol

Description: Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.

Moisture content: Liquid polyethylene glycols are very hygroscopic, solid grades, e.g. PEG 4000 and above, are not hygroscopic.

Solubility: All grades of polyethylene glycol are soluble in water. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Functional Category: Ointment base; plasticizer; suppository base; tablet and capsule lubricant

Applications: Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. Solid grades are generally employed in topical ointments; Mixtures of polyethylene glycols can be used as suppository bases,

Storage: Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Incompatibilities: all grades can exhibit some oxidizing activity, liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

5.2.9 Propylene Glycol[41]

Synonyms

1, 2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1, 2-diol; propylenglycolum.

Chemical Name: 1, 2-Propanediol

Nonproprietary Names

BP: Propylene Glycol

JP: Propylene Glycol

PhEur: Propylene Glycol

USP: Propylene Glycol

Description: Propylene glycol is a clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acrid taste resembling that of glycerin. Solubility Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Functional Category: Antimicrobial preservative; disinfectant; humectants; plasticizer; solvent; stabilizing agent; water-miscible cosolvent.

Applications: Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

Storage: At cool temperatures, propylene glycol is stable in a well-closed container; it is hygroscopic and should be stored in a well closed container, protected from light, in a cool, dry place.

Incompatibilities: Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

5.2.10 Titanium Dioxide[44]

Synonyms: Anatase titanium dioxide; brookite titanium dioxide; color index number 77891; E171; Hombitan FF-Pharma; Kemira AFDC; Kronos 1171; pigment white 6; Pretiox AV-01-FG; rutile titanium dioxide; Tioxide; TiPure; titanic anhydride; titanii dioxidum; Tronox.

Nonproprietary Names

BP: Titanium Dioxide

JP: Titanium Oxide

PhEur: Titanium Dioxide

USP: Titanium Dioxide

Chemical Name: Dioxotitanium

Description: White, amorphous, odorless, and tasteless nonhygroscopic powder. Although the average particle size of titanium dioxide powder is less than 1 mm, commercial titanium dioxide generally occurs as aggregated particles of approximately 100 mm diameter. Titanium dioxide may occur in several different crystalline forms: rutile; anatase; and brookite. Of these, rutile and anatase are the only forms of commercial importance. Rutile is the more thermodynamically stable crystalline form, but anatase is the form most commonly used in pharmaceutical applications.

Moisture content: 0.44%

Solubility: Practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvents, and water. Soluble in hydrofluoric acid and hot concentrated sulfuric acid. Solubility depends on previous heat treatment; prolonged heating produces a less-soluble material.

Functional Category: Coating agent; opacifier; pigment.

Applications: Titanium dioxide is widely used in confectionery, cosmetics, and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment.

Storage: Titanium dioxide should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities: Titanium dioxide has shown to induce photo oxidation of unsaturated lipids.

5.2.11. Dichloromethane

Synonyms: Methylene chloride

Nonproprietary Names

BP: Methylene chloride

PhEur: Methylene chloride

USP: Dichloromethane

Chemical Name: Methylene Dichloride

Description: Clear, colorless, volatile liquid

Moisture content: 0.05% m/m, determined on 10.0gm

Solubility: Sparingly soluble in water miscible with ethanol (96%)

Relative density: 1.320 – 1.332

Refractive index: 1.423 – 1.425

Functional Category: Solvent, Granulation liquid

Applications: Dichloromethane used in pharmaceutical industry as a solvent and analytical reagent.

Storage: In air tight container, protected from light

5.3. COATING POLYMER PROFILE

5.3.1 Polymethacrylates[39]

Synonyms: Acryl-EZE; acidi methacrylici et ethylis acrylatis polymerisatum; acidi methacrylici et methylis methacrylatis polymerisatum; ammonio methacrylatis copolymerum; copolymerum methacrylatis butylati basicum; Eastacryl; Eudragit; Kollicoat MAE; polyacrylatis dispersio 30 per centum; polymeric methacrylates.

Nonproprietary Names

BP: Ammonio Methacrylate Copolymer (Type A)

Ammonio Methacrylate Copolymer (Type B)

Methacrylic Acid–Ethyl Acrylate Copolymer (1: 1)

Methacrylic Acid–Methyl Methacrylate Copolymer (1: 1)

Methacrylic Acid–Methyl Methacrylate Copolymer (1: 2)

PhEur: Ammonio Methacrylate Copolymer (Type A)

Ammonio Methacrylate Copolymer (Type B)

Basic Butylated Methacrylate Copolymer

Methacrylic Acid–Ethyl Acrylate Copolymer (1: 1)

Methacrylic Acid–Methyl Methacrylate Copolymer (1: 1)

Methacrylic Acid–Methyl Methacrylate Copolymer (1: 2)

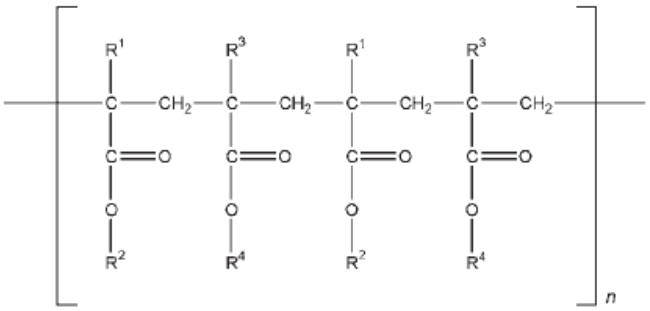
USP-NF: Amino Methacrylate Copolymer

Ammonio Methacrylate Copolymer

Methacrylic Acid Copolymer

Chemical Name: Poly (methacrylic acid, methyl methacrylate)

Structure:



Description: Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. Eudragit L and S, referred to as methacrylic acid copolymers in the USP32–NF27 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1: 1 in Eudragit L (Type A) and approximately 1: 2 in Eudragit S (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer. Eudragit L 100-55 (prepared by spray-drying Eudragit L 30 D- 55) is a white, free-flowing powder that is redispersible in water to form latex that has properties similar to those of Eudragit L 30 D- 55.

Viscosity (dynamic): 50–200 mPa s for Eudragit L and S; 415 mPa s for Kollicoat MAE 100 P

Solubility: soluble acetone, alcohol and in gastric fluid to pH 5.0 and 5.5

Functional Category: Film-forming agent; tablet binder; tablet diluent.

Applications: Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.(1–21) Depending on the type of polymer used, films of different solubility characteristics can be produced; Eudragit L, used as enteric coating

agents because they are resistant to gastric fluid. Different types of enteric coatings are soluble at different pH values: e.g. Eudragit L is soluble at pH > 6 whereas Kollicoat MAE 100 P, commercially available as redispersible powder forms, which are designed for enteric coating of tablets or beads.

Storage: Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C. Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C.

Incompatibilities: Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; Kollicoat MAE 100 P is incompatible with magnesium stearate.

6. MATERIALS AND EQUIPMENTS

6.1. TABLE 5: **List of Materials**

S.No	Materials	Manufacturers and suppliers
1	Diclofenac sodium	Sigma Aldrich, Bangalore
2	Ethyl cellulose	Lab chemicals, Chennai
3	Povidone (PVP – K30)	Lab chemicals, Chennai
4	Microcrystalline cellulose	Paxmy specialty chemicals, Chennai
5	Lactose anhydrous	Chemspure, Chennai
6	Eudragit L100	BASF,Germany
7	Kollicoat MAE 100P	BASF,Germany
8	Propylene glycol	Lab chemicals,Chennai
9	Titanium dioxide	Sigma Aldrich,Bangalore
10	Polyethylene glycol	Chemspure,Chennai
11	Methylene chloride	Sigma Aldrich,Bangalore
12	Isopropyl alcohol	Sigma Aldrich,Bangalore
13	Purified Talc	Chemspure, Chennai
14	Sunset yellow	Sigma Aldrich, Bangalore
15	Hydrochloric acid	S.d. Fine chemicals ltd, Mumbai
16	Sodium hydroxide	S.d. Fine chemicals ltd, Mumbai
17	Potassium di hydrogen phosphate	S.d. Fine chemicals, Mumbai
18	Potassium chloride	Chemspure, Chennai
19	Ethanol	S.d. Fine chemicals, Mumbai

6.2. TABLE 6: **List of Equipments**

S.No	Equipments	Manufacturer
1	Digital balance	Axis LE/GC, India
2	Digital pH meter Model 111E	Electrolab, Mumbai
3	UV – visible spectrophotometer	Shimadzu UV – 1601, Japan
4	FT – IR spectrophotometer MB 104	Shimadzu corporation,japan
6	Dissolution tester	Electrolab TDT – 08L, Mumbai
7	Hot air oven	Minicon, Mumbai
8	Humidity cabinet	Sigma instruments, Mumbai
9	High precision balance	Infra, India
10	Friabilator (USP) EF 2	Electrolab, Mumbai
11	Laboratory centrifuge 2C	Remi, India
12	Table sieve shaker CAT. 510	Secor, India
13	Screw feed Extruder	
14	Marumerizer	
15	Coating pan	
16	Differential scanning calorimetry	

7. FORMULATION AND EVALUATION

7.1. Preparation of Diclofenac Sodium Core Pellets

1) Sifting **:** Diclofenac sodium, microcrystalline cellulose PH 101, Lactose were sifted through 24# SS screen mesh and transferred to planetary mixer (PLM 200).

2) Mixing **:** The materials of stage 1 were mixed thoroughly for 30 minutes in a planetary mixer. 10% of mixed materials is taken out for dusting purposes in the forthcoming marumarization stage

3) Binder preparation **:** Povidone K 30 was prepared as 9% w/v solution with the help of water. The binder solution of stage 3 was added to stage 2 and until a cohesive mass was obtained.

4) Extrusion **:** The cohesive mass prepared at stage 3 was loaded to Screw-feed extruder using 0.9mm mesh screen. Adjustments are made in the machine and the cohesive mass prepared was obtained as vermicelli type extrusions.

5) Marumarization **:** The prepared extrudates were passed to marumerizer and operated at a speed of 1400 rpm for 4-6 minutes. 10% of stage I materials were used as dusting powder. Operation was continued until good spherical pellets are obtained

6) . **Drying** **:** The pellets obtained in stage 5 dried at 4^{0o} C for 3 hours in fluidized bed dryer. The pellets were kindled at the interval of one hour to ensure uniform drying.

7) Sizing **:** Dried pellets were passed through 12# and fraction retained on 24# was collected for further characterization.

SCHEMATIC REPRESENTATION OF FABRICATION METHODOLOGY

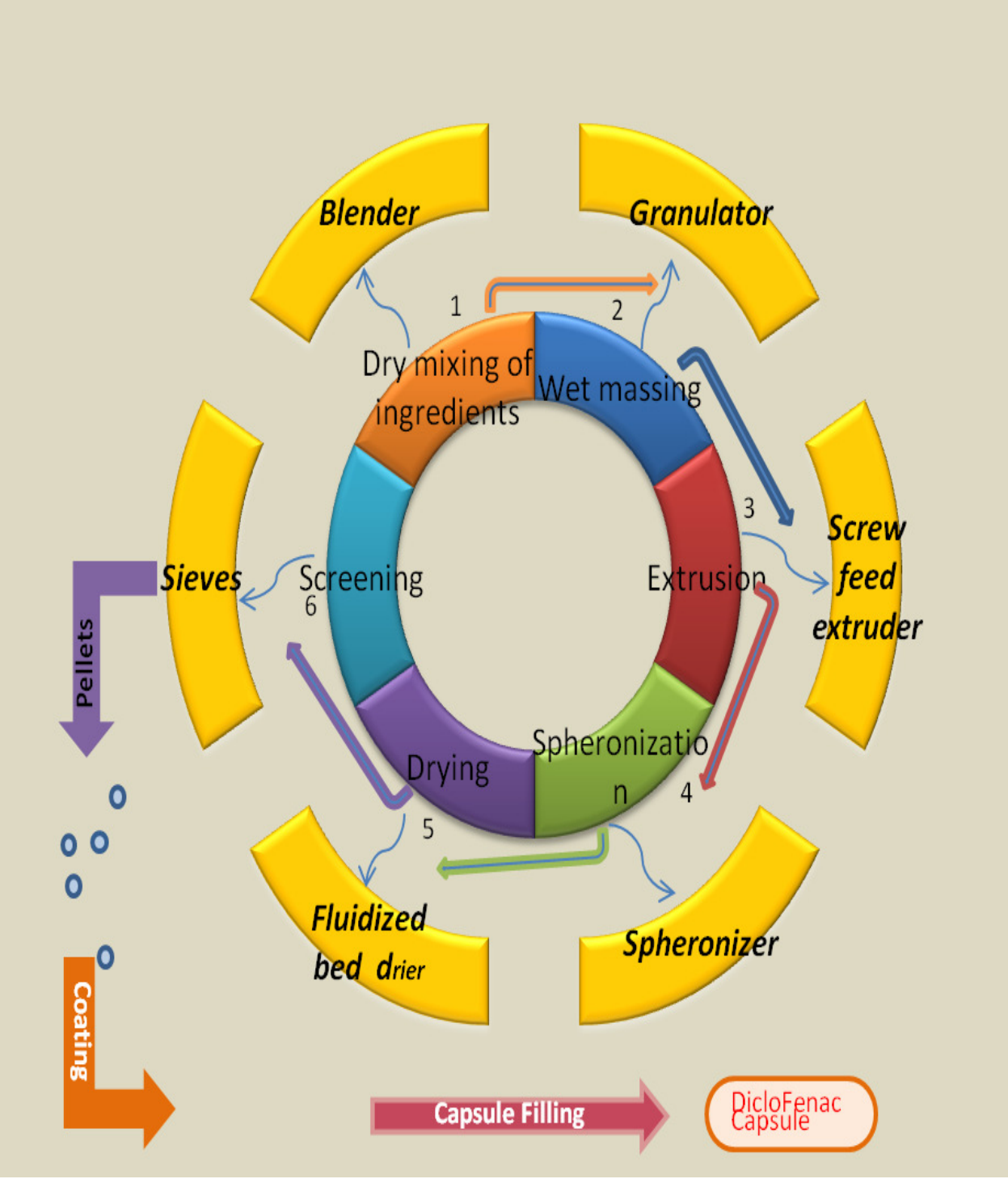


TABLE 7: **Formulation of Diclofenac Sodium Core Pellets**

S.NO	INGREDIENTS	F1 (mg/cap)	F2 (mg/cap)	F3 (mg/cap)	F4 (mg/cap)	F5 (mg/cap)	F6 (mg/cap)
1.	**DICLOFENAC SODIUM**	100	100	100	100	100	100
2.	**MICRO CRYSTALLINE CELLULOSE**	66	79	92	105.60	99	99
3.	**POVIDONE K30**	3.3	6.6	9.9	13.2	9.9	9.9
4.	**LACTOSE**	160.7	144.4	128.1	111.20	128.10	128.10
5.	**TOTAL**	330	330	330	330	330	330

From formulation 1 (F1) to formulation 6 (F6), excipients were altered at different concentration to obtain desired pellets, while the active pharmaceutical ingredient was kept constant in all the formulations.

Where,

mg - milligrams; Cap - Capsule

FIGURE 9: **Extrudates of Diclofenac Sodium**

(A)

(B)

(C)

Where, A Depicts Screw feeder extruder, B Depicts Processing extrudate, C Depicts Finished Extrudate

7.1.1. Coating Methodology for Pellets

TABLE 8: **Formulation For Coating with Kollicoat MAE 100P**

INGREDIENTS	C1 (mg/cap)	C2 (mg/cap)	C3 (mg/cap)	C4 (mg/cap)
KOLLICOAT MAE 100P	33.0	33.0	49.5	49.5
ETHYL CELLULOSE	_	6.6	_	6.6
PROPYLENE GLYCOL	6.75	6.75	6.75	6.75
TITANIUM DIOXIDE	1.5	1.5	1.5	1.5
TALC	12	12	12	12
SUNSET YELLOW	1.5	1.5	1.5	1.5
PURIFIED WATER	0.25	0.25	3.75	3.75
ISOPROPYL ALCOHOL	_	33.0	_	33.0
METHYLENE DI CHLORIDE	_	33.0	_	33.0

STEP 1: ***Preparation of polymer suspension:***
Kollicoat MAE 100P is dispersed in specified amount of water. When it is completely dispersed the plasticizer propylene glycol is incorporated.

STEP2: Preparation of pigment suspension:
Sunset yellow, titanium dioxide and talc are intensively stirred into specified amount of water and homogenized.

STEP3: Preparation of final solution
The pigment suspension is stirred into the coating suspension .The spray suspension must be stirred during spraying to prevent the solid substances settling out.

STEP 4: Preparation of sub coating solution:

Weighed quantity of ethyl cellulose was dissolved in isopropyl alcohol and methylene dichloride in 1:1 ratio as sub coat solution. Prepared sub coat solution sprayed to the pellets prior to enteric coating process.

TABLE 9 : **Formulation For Coating With Eudragit L 100**				
INGREDIENTS	**C5 (mg/cap)**	**C6 (mg/cap)**	**C7 (mg/cap)**	**C8 (mg/cap)**
EUDRAGIT L 100	33.0	33.0	49.5	49.5
ETHYL CELLULOSE	_	6.6	_	6.6
POLY ETHYLENE GLYCOL 6000	6.75	6.75	6.75	6.75
TITANIUM DIOXIDE	1.5	1.5	1.5	1.5
TALC	12	12	12	12
SUNSET YELLOW	1.5	1.5	1.5	1.5
ACETONE	0.220	0.220	0.220	0.220
ISOPROPYL ALCOHOL	0.330	33.330	0.330	33.330
METHYLENE DI CHLORIDE	_	33.0	_	33.0

Preparation of EUDRAGIT L 100 enteric coating solution:

STEP 1: Preparation of diluents mixture:
Diluent mixture is prepared by mixing specific quantities of acetone and isopropanol as per the table no: 9

***STEP2: Preparation of Eudragit solution*:**
Specified amount of Eudragit L 100 is added slowly into 50% of diluent mixture and stirred for 30-60 minutes until the polymer is completely dissolved.

STEP3: Preparation of excipients suspension
Specified amount of talc and plasticizer poly ethylene glycol 6000 is added to remaining diluents mixture and stirred for 10 minutes in high shear mixer.

STEP4: Preparation of final enteric coating solution
The excipient suspension is poured slowly into Eudragit solution while it is stirred with a stirrer. Finally the spray suspension is passed through 0.5 mm sieve and used for coating.

TABLE 10: **COATING SPECIFICATIONS**

S.NO	COATING PARAMETERS	KOLLICOAT MAE 100P	EUDRAGIT L 100
EQUIPMENT SET UP			
1.	COATING PAN	8"STAINLESS STEEL COATING PAN	8"STAINLESS STEEL COATING PAN
2.	SIZE OF BATCH	1 KG	1KG
3.	DRUM SPEED	8-10rpm	8-10 rpm
4.	NUMBER OF SPRAY GUNS	1	1
5.	NOZZLE BORE	1.2 mm	1.2 mm
6.	DISTANCE PELLET BED/SPRAY GUN	10 cm	10cm
PROCESS DATA			
7.	INLET AIR TEMPERATURE	60 ^{o} C	50 ^{o} C
8.	EXHAUST AIR TEMERATURE	25 ^{o} -30 ^{o} C	25 ^{o} -30 ^{o} C
9.	PRODUCT TEMPERATURE	32 ^{o} -35 ^{o} C	25 ^{o} -30 ^{o} C
10.	SPRAY RATE	40 g/min	3-6 g/min
11.	FINAL DRYING AT 40 C	2 hrs	2 hrs

PHOTOGRAPHS OF PREPARED DICLOFENAC SODIUM CORE AND ENTERIC COATED CAPSULES

A) DICLOFENAC SODIUM CORE PELLETS

B) DICLOFENAC SODIUM ENTERIC COATED PELLETS

7.2. EVALUATION PARAMETERS AND PROCEDURE FOR CORE AND ENTERIC COATED PELLETS[33]

Powder flow

Pharmaceutical industry has generated a variety of methods to characterize flow of powder or granules. The development of such a variety of test methods was inevitable; powder behavior is multifaceted and thus complicates the effort to characterize powder flow. In spite of the complications an attempt has been made to characterize the flow property of the powder or granules with these methods. The most frequently used methods are angle of repose, compressibility index and hausner ratio.

7.2.1 Angle of repose

The angle of repose has been used in several branches of science to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles.

Procedure

Angle of repose was done by using a funnel on a fixed base with retaining tip to retain a layer of the powder on the base. Height of the funnel was carefully built up a symmetrical cone of granules and it was freed from vibration. Care was taken to prevent vibration as the funnel is moved. The funnel height was maintained approximately 2- 4 cm from the top of the granules pile as it is being formed in order to minimize the impact of the falling powder on the tip of the cone.

Angle of repose was determined by measuring the height of the cone of powder and calculating the angle of repose

$$\tan\theta = \frac{h}{r}$$

Where,

h = Height of the cone; r = Radius of surface area of the pile.

7.2.2 Bulk density and tapped density:

An accurately weighed quantity of the pellets (w), which was previously passed through 40#, was carefully poured into the graduated cylinder and the volume (v_0) was measured. The graduated measuring cylinder was tapped for 100 times, volume (v_f) was measured and continued the operation till the two consecutive readings were equal. Bulk density and tapped density were calculated using the formula given below,

$$Bulk\ density = \frac{W}{V_0}; \qquad Tapped\ density = \frac{W}{V_f}$$

Where,

W = weight of the pellets; V_0 = initial volume; V_f = final volume

TABLE 11: **Flow properties and corresponding angle of repose**

Flow property	**Angle of repose (degrees)**
Excellent	25 – 30
Good	31 – 35
Fair – aid not needed	41 – 45
Passable – may hung up	41 – 45
Poor – must agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	> 66

7.2.3 Compressibility index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index.

Procedure

Compressibility index of the pellets was determined by measuring both the bulk volume and the tapped volume of the pellets. On preference, measured the unsettled apparent volume $V_{0,}$ and final tapped volume $V_{f,}$ of the pellets until no further volume changes occur on tapping using 250ml volumetric cylinder with 100g of pellets. The compressibility index was calculated with the following equation,

$$compressibility\ index = 100\ X\ \left(\frac{(V_0 - V_f)}{V_0}\right)$$

Alternatively, the compressibility index can be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) by following equation

$$compressibility\ index = 100\ X\ \left(\frac{(\rho_{tapped} - \rho_{bulk})}{\rho_{tapped}}\right)$$

7.2.4 Hausner's ratio

It is a number that is correlated to the Flowability of the powder or granular material. In recent years the hausner ratio has become the simple, fast, and popular methods of predicting powder flow characteristics.

Procedure

The hausner ratio and compressibility index are determined by measuring both the bulk volume and the tapped volume of the powder. Hausner's was calculated with the following formula.

$$Hausner\ ratio = \frac{V_0}{V_f}$$

Alternatively it can be calculated by following equation,

$$Hausner\ ratio = \frac{\rho_{tapped}}{\rho_{bulk}}$$

TABLE 12: **Scale of Flowability**

Compressibility index (%)	**Flow character**	**Hausner ratio (g/ml)**
<10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.49
>38	Very, very poor	>1.60

7.2.5 Friability: [15]

Friability of pellets were tested using an ***Abrasion drum*** which is a modified USP friability tester .This drum can generate two different types of motion depending on how the abrasion drum is mounted to the friabilator arm. One motion generates cascading movement from one lamella to other, while the other motion raises and drops the spheres from a distance approx 200 mm.

Procedure

10 gm of pellets are weighed initially and taken as w_1, placed in a friabilator and rotated for 25 rpm for 10 minutes. Pellets were re-weighed after the removal of fines and noted as w_2. The percentage of weight loss was calculated by the following equation. As per the IP official limit friability should not be more than 1%

$$\textbf{Percentage friability} = \frac{(W1 - W2)}{W1} \textbf{ X 100}$$

Where, w_1 = Initial weight of pellets; w_2 = Final weight of pellets

7.2.6 Sieve analysis: [32]

The sieves used in analysis were weighed individually. Sieve number 18, 20, 24 were used for analysis.100 gm of sample weighed separately. Sieves were cleaned and assembled in ascending order of sieve numbers (18, 20, and 24). A receiving pan was placed below 24# sieve. Carefully the sample is placed onto the top sieve. The sieve stack is placed in mechanical shaker and operated for 10 minutes. The stack is removed from shaker and weight of each sieve with its retained sample was weighed.

The percentage of sample retained in each sieve is calculated by formula:

$$\% \text{ Retained} = \frac{Mass\ retained\ in\ each\ sieve}{Total\ mass\ of\ sample\ taken}$$

The percentage of sample passed from each sieve is calculated by formula:

$$\% \text{ Passing} = 100 - \% \text{ Retained}$$

7.2.7 Loss on drying: [25]

One gm of pellets was weighed in a petriplate and noted it as S1. Weighed pellets were dried in oven for three hours at 105° C. After three hours petriplate was taken out and reweighed and noted it as S2. The percentage of weight loss after drying was calculated as per the following formula,

$$\text{Percentage loss} = \frac{weight\ loss(S2-S1)}{initial\ weight\ of\ sample(S1)} \times 100$$

Where, **S2-S1 = Weight loss of the pellets**

S2 = Weight of sample after drying

S1 = Weight of sample before drying

7.2.8 Drug content [10]

Weigh initially 5 gm of sample, crushed the pellets in a mortar and **weighed** accurately a quantity equivalent to 50 mg of Diclofenac sodium and shaken with 60 ml of methanol in 200 ml volumetric flask and diluted the volume with methanol. 5ml of this solution is diluted to 100 ml with methanol. The absorbance of resulting solution is

measured at maximum about 285 nm. The content of Diclofenac sodium is calculated from the absorbance obtained by repeating the procedure using Diclofenac sodium RS in place of substance.

7.3 EVALUATION OF CAPSULES FILLED WITH DICLOFENACSODIUM CORE PELLETS

7.3.1Weight variation [61]

Twenty capsules were selected at randomly, weighed individually and an average weight is calculated. Not more than two capsules should deviate from average weight by more than the percentage given in standard table no 13 and none of the capsule should deviate by more than double the percentage given in standard table as per I.P.

TABLE 13: **I.P.OFFICIAL LIMITS**

S.NO	Average weight of capsule	Percentage variation
1.	More than 300 mg	±7.5%
2.	Less than 300 mg	±10%

7.3.2 Drug content [10]

Randomly selected 10 capsules from a trial emptied the contents into a mortar. Crushed contents were weighed accurately a quantity of powder equivalent to 50 mg of Diclofenac sodium was shaken with 60 ml of methanol in 200 ml volumetric flask and diluted the volume with methanol. 5ml of this solution is diluted to 100 ml with methanol. The absorbance of resulting solution is measured at maximum about 285 nm. The content of Diclofenac sodium is calculated from the absorbance obtained by repeating the procedure using Diclofenac sodium RS in place of substance under examination. I.P Limit for assay is 90-110%.

7.3.3 Content uniformity

To ensure the consistency of dosage units, each unit should have drug content within a narrow range around the label claim. Content uniformity is defined as degree of uniformity in amount of drug substance among dosage units.

Procedure

Ten capsules were randomly selected from each trial; contents were removed from each capsule and assayed individually. The percentage of drug present in each individual capsule is calculated. All the capsules should comply the test and should be within I. P Limit. Limit is 90-110%.

7.3.4 *Invitro* dissolution test

Dissolution studies were carried out by USP type I method at 37±5^{o}C, taking 900 ml of phosphate buffer of pH 6.8 at 50 rpm. The test sample of 5ml was withdrawn at specific interval (15, 30, and 45 minutes) and replaced with fresh dissolution medium. The test sample was filtered and diluted with 100 ml of buffer medium. The concentration of dissolved drug was determined using U.V. spectrophotometer at 285 nm. These results are given in table no: 23

7.4 EVALUATION OF CAPSULES FILLED WITH DICLOFENACSODIUM ENTERIC COATED PELLETS:

7.4.1 Weight variation

Twenty capsules were selected at random ,weighed individually and an average weight is calculated not more than two capsules deviate from average weight by more than the percentage given in standard table and none of the capsule deviates by more than double the percentage given in standard table no: 14

TABLE 14: **I.P.OFFICIAL LIMITS**

S.NO	Average weight of capsule	Percentage variation
1.	More than 300 mg	±7.5%
2.	Less than 300 mg	±10%

7.4.2 Drug content

Randomly selected 10 capsules from a trial emptied the contents into a mortar. Crushed the contents and weighed accurately a quantity of powder equivalent to 50 mg of Diclofenac sodium ,shaken with 60 ml of methanol in 200 ml volumetric flask and diluted the volume with methanol. 5ml of this solution is diluted to 100 ml with methanol. The absorbance of resulting solution is measured at maximum about 285 nm. The content of Diclofenac sodium is calculated from the absorbance obtained by repeating the procedure using Diclofenac sodium RS in place of substance under examination. As per I.P. assay limit is 90 – 110%.

7.4.3 Content uniformity

To ensure the consistency of dosage units, each unit should have drug content within a narrow range around the label claim.

Procedure

Ten capsules were randomly selected from each trial; contents were removed from each capsule and assayed individually. The percentage of drug present in each individual capsule is calculated. All the capsules should comply the test and within I. P Limit. Limit is 90-110%

7.4.4 *In vitro* dissolution test

In vitro dissolution studies were carried out using USP Type I apparatus at 50 rpm. The dissolution medium consisted of 900 ml pH 0.1N Hydrochloric acid buffer for first two hours and then it was replaced with 900ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C. Withdrawn suitable volume of test solution and it was replaced with fresh buffer, absorbance was measured at 285 nm.

7.4.5 Scanning electron microscopy49

Scanning electron microscopy is an electron optical imaging technique that yields both topographic images and elemental information. SEM is useful for characterizing the size and morphology of microscopic specimens. Typically SEM analysis requires a small amount (10^{10}-10^{12}) of solid specimen that is coated with conductive substance to inhibit sample charging.

The sample is placed is placed in evacuated chamber and scanned in raster pattern by electron beam. Interaction of electron beam with specimen produces a variety of physical phenomena that, when detected, used to form images and provide elemental information. These phenomena include (1) emission of secondary electrons (2) Reflection of back scattered electrons.(3) Characteristic X-Ray emission (4)Emission of auger electrons (5)Cathadoluminescence (6) Conduction of current (7) Charging from induced voltages (8)Electron- transmission (9) Heat generation and (10) Electromotive forces.

Procedure

The particle size and morphology of Diclofenac sodium Core and Enteric Coated pellets were analyzed through SEM Analysis. Samples from final optimized batches of core and coated pellet formulations (F6 & C8) were mounted on aluminium stubs using double sided sticky tape, vaccum coated with gold film (Polaron SC 500 sputter coater) and examined using Scanning Electron Microscope (Leo Stereoscan S-360).

7.5. STABILITY STUDIES

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within is physical, chemical, therapeutics and toxicological specifications. Stability studies were conducted for the optimized enteric coated pellet formulation. The reason for selection is, formulation have shown good results in *invitro* drug release studies. The stability was performed as per following.

7.5.1 Preliminary stability of the optimized batch

The optimized batch (C8) was charged on accelerated stability as per ICH guidelines.

TABLE 15**: Stability protocol of enteric coated Diclofenac sodium capsules**

S.No	Study	Storage condition
1	Long term	25°C ± 2°C / 60% RH ± 5% RH
2	Intermediates	30°C ± 2°C / 60% RH ± 5% RH
3	Accelerated	40°C ± 2°C / 75% RH ± 5% RH

7.5.2 Testing parameters: Appearance, colour change, friability and drug content was tested after a period of 60 days.

8. RESULTS AND DISCUSSION

In the present work Capsule dosage form containing Diclofenac sodium enteric coated pellets were prepared by using Extrusion – Marumarization technique for the fabrication of Diclofenac sodium pellets and enteric coated with enteric polymer for the treatment of Osteoarthritis and Rheumatoid arthritis.

8.1. Preformulation

Preformulation data are vital for decision making on the choice of dosage form and excipients and essential for preceding it further for the development of dosage form.

8.1.1. Characterization of active pharmaceutical ingredient and polymer

Drug (Diclofenac sodium), Diluents (MCC Ph101), Binder (PVP K30), Filler (Lactose), were characterized by using Fourier Transform Infra Red Spectroscopy.

Diclofenac sodium was analyzed under IR spectra and their results were produced in figure no: 10. The mixture of API with Lactose, API with PVP K30, API with MCC, and their mixture were characterized through IR spectrum and their spectra were given in figure no: 11, 12, 13 and 14 respectively. The resulted IR spectra were interpreted and presented. The results match the test sample when compared with reference standard.

TABLE 16: **Interpretation of IR Spectrum for Diclofenac Sodium**

S.NO	Functional group	Wave number cm^{-1}
1	NH Stretching	3209.66-3446.91
2	CH Bend in plane	1400.37-1456.30
4	C=C	1504.53-1572.04
5	C-C Stretching	840.99-1089.82
6	C-NH	1180.47-1296.21
7	Cl_2	624.96-750.33

Diclofenac sodium showed a prominent IR absorption band in the region of 3209.66, 3446.91 cm-1 due to urea NH stretching, a very sharp peak observed at 1400.37, 1456.30cm^{-1} due to –CH Bend in plane of Benzene ring, at 1504.53, 1572.04 cm^{-1} the absorption was due to C=C, a strong absorption band s at 840.99-1089.82 cm^{-1} due to C-C Stretching, at 1180.47-1296.21 cm^{-1} due to C-NH was observed. The absorption peak of chlorine occurred at 624.96, 750.33 cm^{-1}.

8.1.2 Thermal analysis for characterizing interaction between drug and excipients

Differential scanning calorimetry was done for the crude drug and its mixture with excipients. The resulted spectra with their melting points were given in figure no: 15 & 16 respectively. Result showed there were presence of an exothermic peak at 285.43° C this attributes to the presence of Diclofenac sodium shown in figure no:15, thermal curve for mixture of drug and excipients exhibited a sharp exothermic effect, at 164.31° C, 216.44, 269.27. These DSC curves indicate the melting points of for polyvinyl pyrolidone, Micro crystalline cellulose and Lactose. DSC results indicate there were presence no interactions between the drug and excipients.

8.1.3 Analysis of Drug Excipient compatibility studies

The drug-excipient compatibility studies were determined in 1:1 ratios under Humidity Cabinet at different temperature and humidity conditions for the period of four weeks and the results showed that there was no physical change in appearance, color and odor. The results were given in table no: 17

FIGURE 10: **FT - IR Spectral Analysis for Diclofenac Sodium**

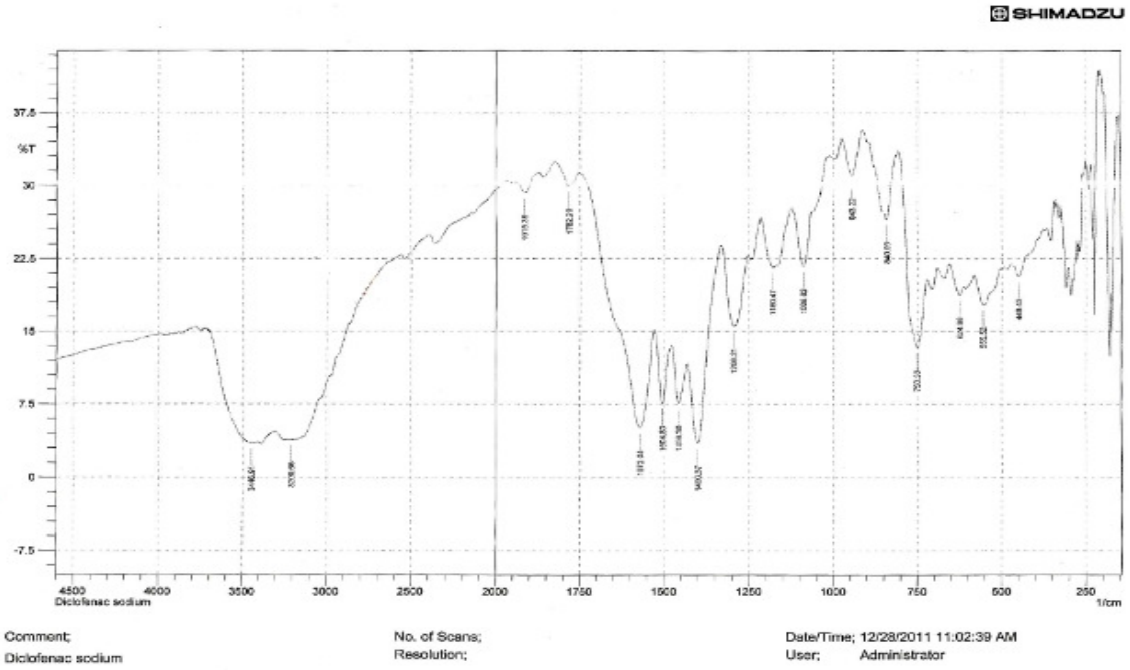


FIGURE 11: **FT - IR Spectral Analysis for Diclofenac Sodium with Lactose**

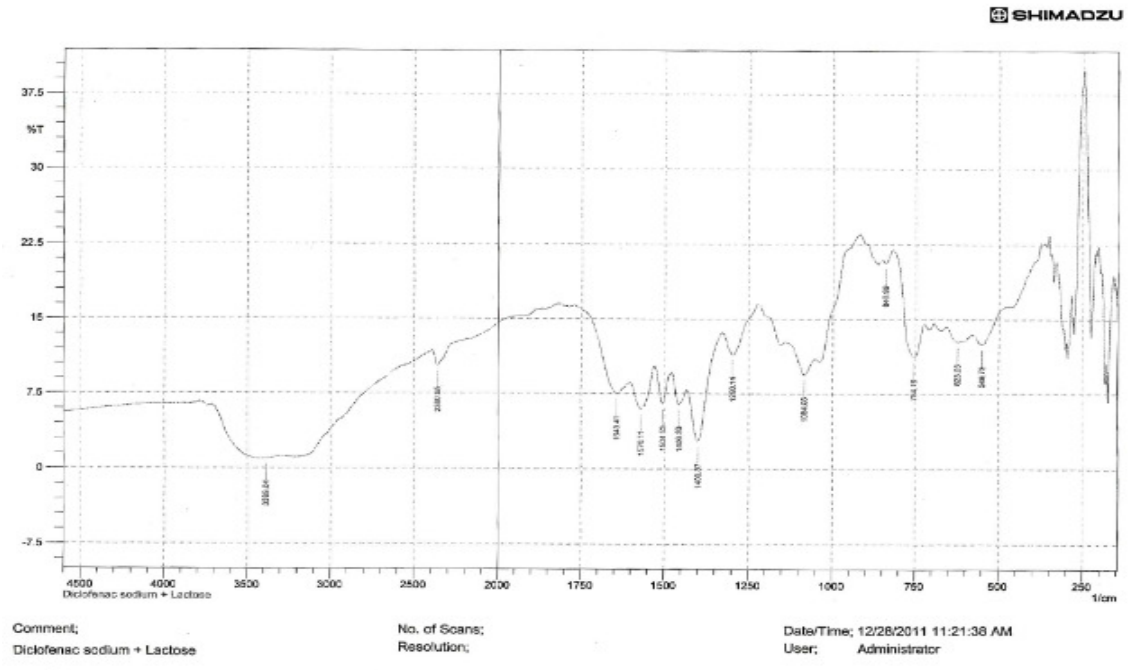


FIGURE 12: **FT - IR Spectral Analysis for Diclofenac Sodium with Microcrystalline cellulose**

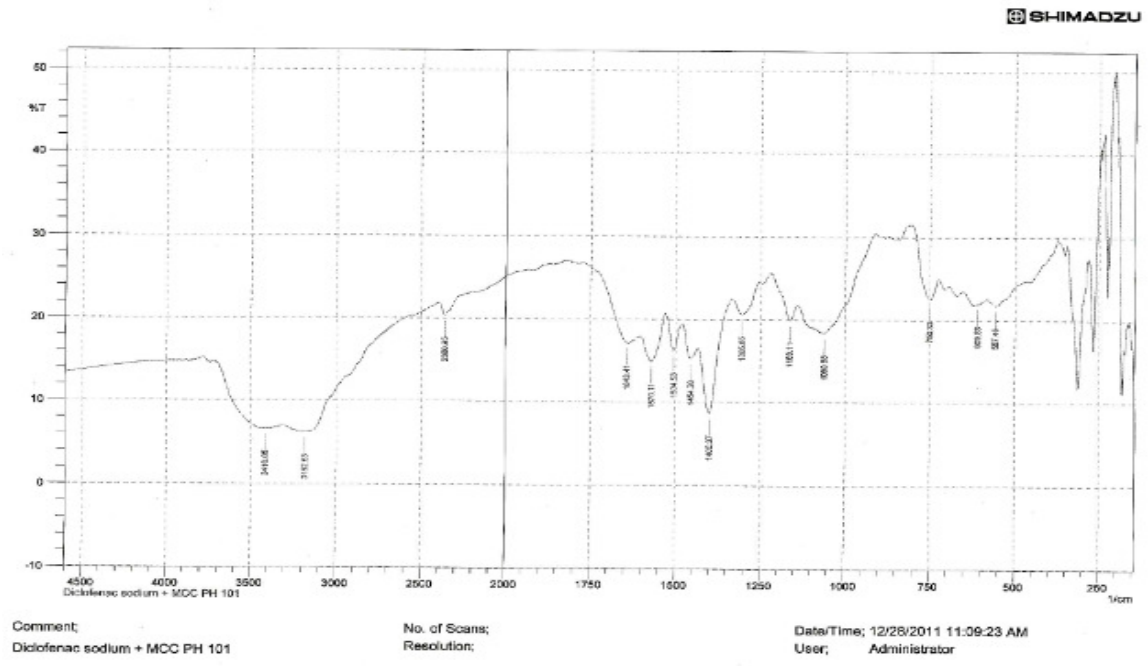


FIGURE 13: **FT - IR Spectral Analysis for Diclofenac Sodium with PovidoneK30**

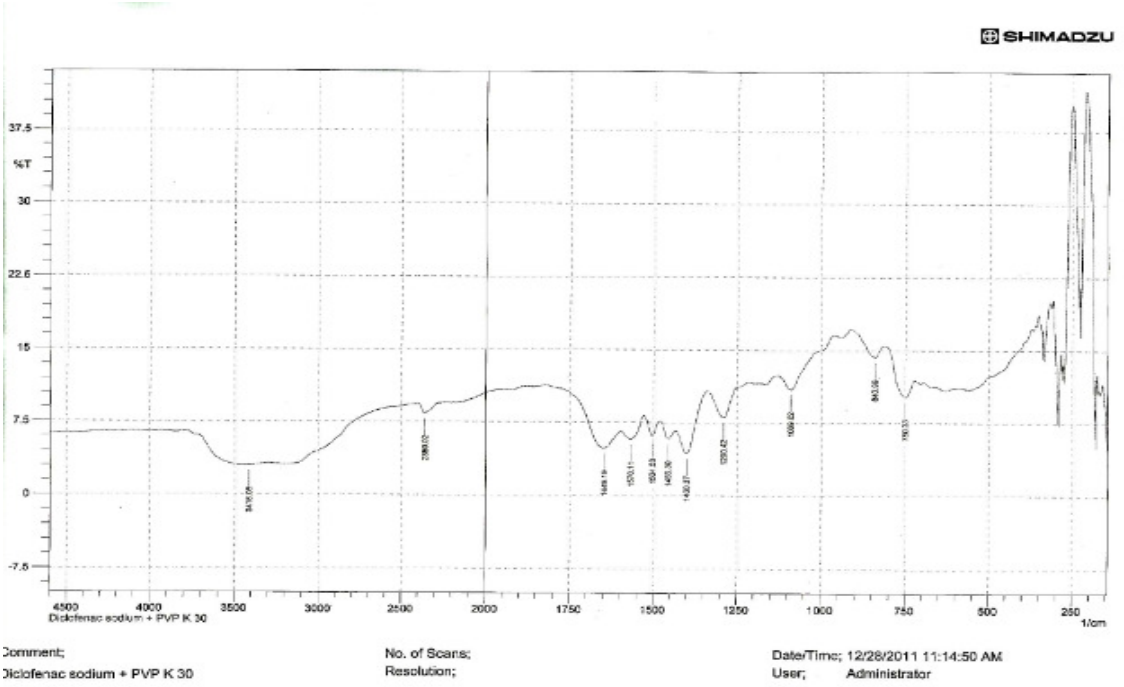


FIGURE 14: **FT - IR Spectral Analysis for Diclofenac Sodium with Microcrystalline cellulose, polyvinyl pyrolidone and Lactose**

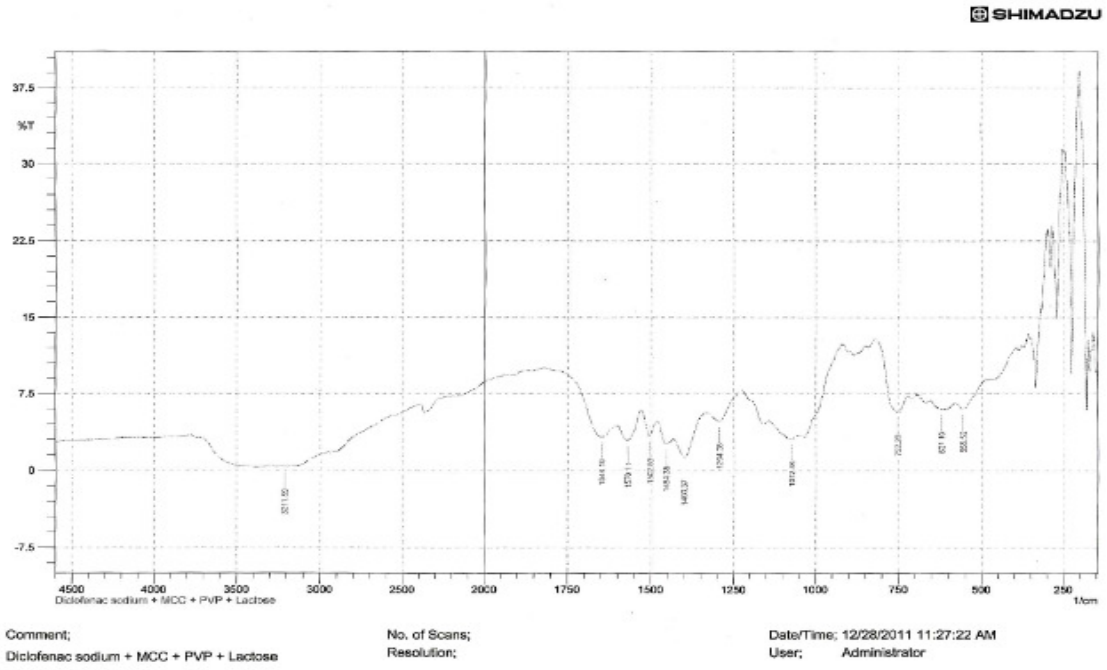


FIGURE 15: **Differential Scanning Calorimetry Spectral Analysis of Diclofenac Sodium**

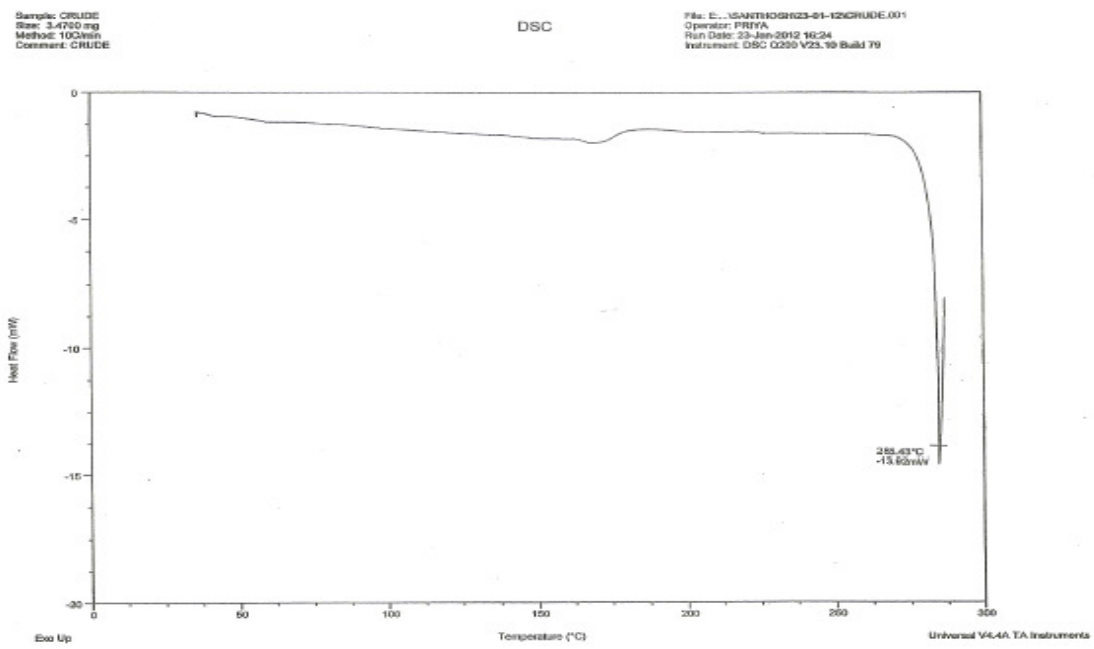


FIGURE 16: **Differential Scanning Calorimetry Spectral Analysis of Diclofenac Sodium with Excipient mixture**

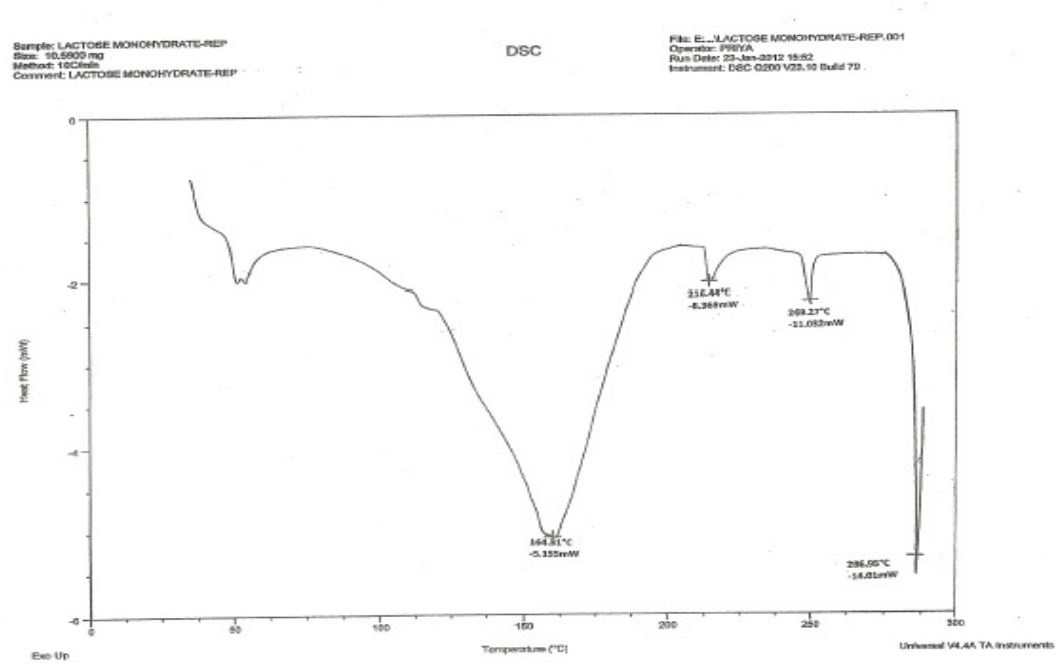


Table 17: **Analysis of Excipients Compatibility by Stability Studies**

S.NO	DRUG + EXCIPIENT	RATIO	INITIAL	CONDITIONS				COMMENTS
				RT40°C/75%RH		RT 60°/90%RH		
				2Weeks	4Weeks	2Weeks	4Weeks	
1	Diclofenac Na + Microcrystalline cellulose pH 101	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
2	Diclofenac Na + Pyro vinyl pyrolidone K 30	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
3	Diclofenac Na+ Lactose monohydrate	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
4	Diclofenac Na + Ethyl cellulose	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
5	Diclofenac Na + Kollicoat MAE 100P	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
6	Diclofenac Na + Eudragit L100	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
7	Diclofenac Na + Titanium dioxide	1:1	White color powder	No colour change	No colour change	No colour change	No colour change	Compatible
8	Diclofenac Na + Talc	1:1	White powder	No colour change	No colour change	No colour change	No colour change	Compatible
9	Diclofenac Na+ Sunset yellow	1:1	Orange colour powder	No colour change	No colour change	No colour change	No colour change	Compatible

8.1.4 Standard curve for Diclofenac sodium

Standard curve for Diclofenac sodium were done by ultraviolet spectroscopy within the range of 200 – 400nm.

The results for standard curve of Diclofenac sodium in 0.1N Hydrochloric acid buffer and pH 6.8 phosphate buffer were shown in graph no: 1 & 2 and table no:18 & 19 respectively.

Straight line equation for Diclofenac Sodium in 0.1N Hydrochloric acid buffer;

$$0.4356 = 0.0291\ (15) - 0.0011$$

Straight line equation for Diclofenac Sodium in pH 6.8 phosphate buffer;

$$0.1294 = 0.0086\ (15) + 0.0004$$

TABLE 18: **Calibration Curve of Diclofenac Sodium in 0.1N HCl**

S.NO	Concentration in µ/ml	Absorbance at 285 nm
1.	5	0.144
2.	10	0.290
3.	15	0.435
4.	20	0.580
5.	25	0.729

GRAPH: 1 **Calibration Curve of Diclofenac Sodium in 0.1N Hydrochloric Acid**

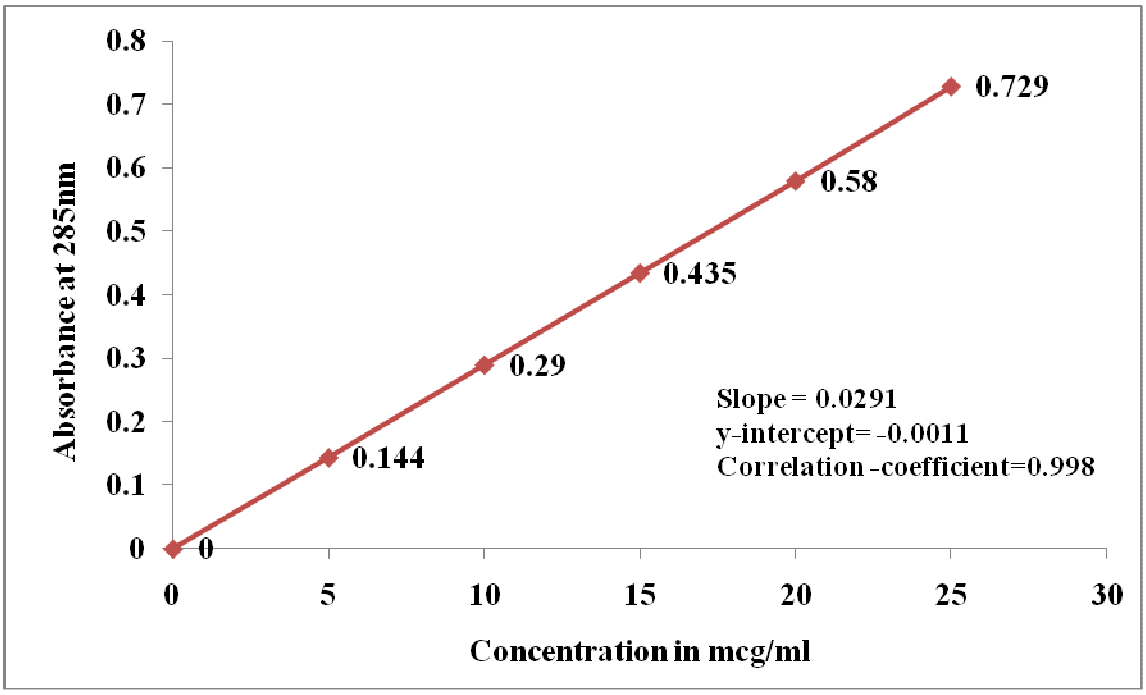
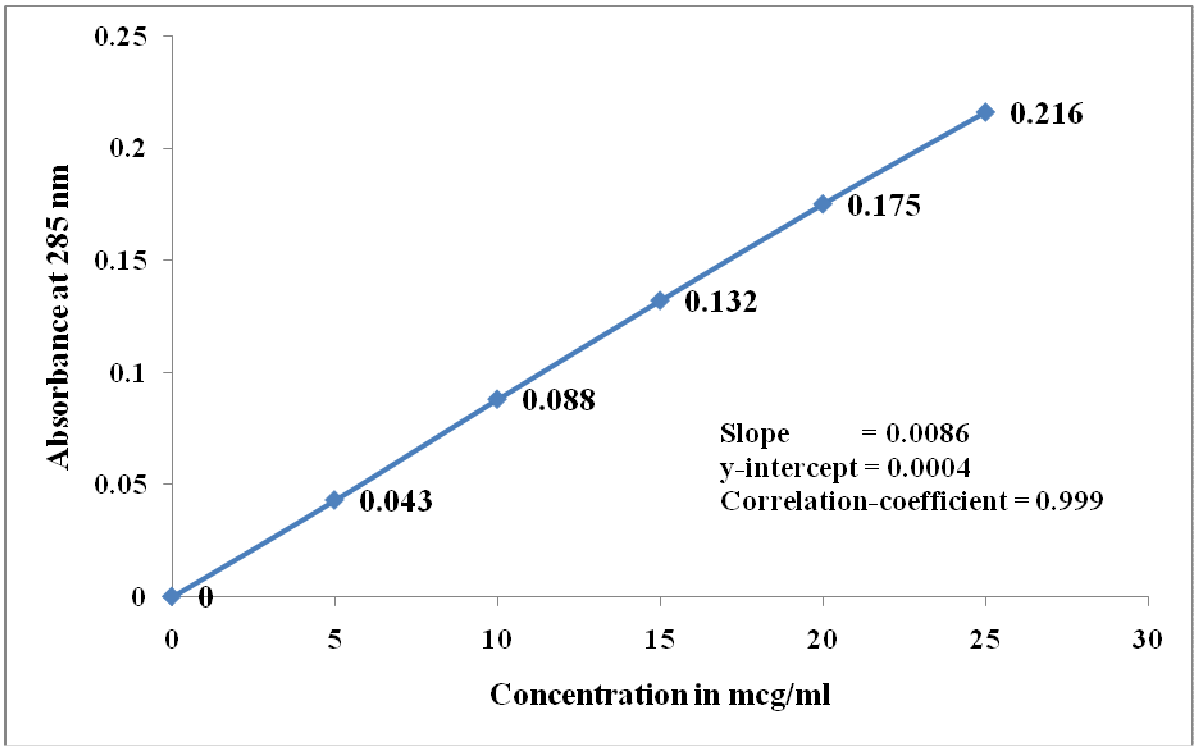


TABLE 19: **Calibration Curve of Diclofenac Sodium in Ph 6.8 Phosphate Buffer**

S.NO	Concentration in µgm/ml	Absorbance at 285 nm
1.	5	0.043
2.	10	0.088
3.	15	0.132
4.	20	0.175
5.	25	0.216

GRAPH: 2 **Calibration Curve of Diclofenac Sodium in Ph 6.8 Phosphate Buffer**



8.2. Evaluation of Core Pellets (F1-F6)

The micromeritic properties such as angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio, Sieve analysis for uncoated core pellets were studied. The overall results were tabulated in table no: 20

The pellets formulated from trial F1 found to be sticky .Therefore trial F1does not supported for further studies. The bulk density and tapped density of formulations F2-F6 ranged from 0.588 to 0.754gm/ml,0.675 to 0.785 gm/ml respectively. The angle of repose of the formulations F1-F6 was found in the range between 52.56 -26.56. Among those formulations F4, F5and F6 shows good and excellent flow character, while F2 and F3shows poor flow.

The percentage of Carr's index was found to be 22.94, 16.45 and 10.57, 9.09 and 8.98. Formulation F2shows passable, F3 and F4 shows fair, F5and F6 shows excellent flow characteristics.

Hausner's ratio ranged from 1.34-1.06 and the formulations F2, F3, F4, F5, and F6 depicts the results 1.34, 1.19, 1.06, 1.04, 1.02. Among this five formulation F4, F5and F6 showed excellent flow character F2 and F3 showed fair and passable flow character.

Sieve analysis was performed in a sieve shaker with a set of sieves (18, 20, and 24) to determine the percentage of pellets obtained during the process. Trial F2 shows 8.4 % in mesh 18, 3.4% in mesh 20 and 88.2% in mesh no: 24. The pellets were not even in size and irregular in shape and size. Maximum quantity of sample retained in mesh no: 24. From trial F3-F6 the percentage of sample retained in mesh no 18 found to be 7.9, 2.5, 1.9, and 1.4. The size and shape of pellets were uniform. In mesh no: 20 the value ranges from 2.8 - 1.5 in mesh no: 24 the formulation F3, F4, F5 and F6 depicts the results of 89.3, 96.1, 97.1, and 97.0%. From the results the size of the pellets assumed to lie between 1.00mm - 0.710 µm as per U.S.P.

The friability tests were performed in abrasive drum and the value ranges from 0.964-0.160 .The values depicts friability is within and passes I.P limit which is not more than 1% w/w, indicating sufficient mechanical integrity and strength for prepared pellets.

The value of loss on drying was checked for the formulations F2-F6. It ranges from 5.42-0.97. Formulations F4, F5 and F6 comply as per I.P limit which is less than 1%.

Drug content of formulation F2-F6 was found to be 97.65, 97.86, 96.59, 99.45, and 101.80. The results shows all formulation containing drugs were within the limit (90-110%) as per I.P and the results were given in the table no : 20

TABLE 20: **Evaluation of Core Pellets**

S.No	FORMULATION	F1	F2	F3	F4	F5	F6
1	ANGLE OF REPOSE(degrees)	-	52.56	43.61	30.68	27.12	26.56
2	BULK DENSITY(gm/ml)	-	0.588	0.645	0.714	0.754	0.749
3	TAPPEDDENSITY(gm/ml)	-	0.675	0.689	0.740	0.785	0.764
4	CARR'S INDEX (%)	-	22.94	16.45	10.57	9.09	8.98
5	HAUSNER'S RATIO	-	1.34	1.19	1.06	1.04	1.02
6	LOSS ON DRYING (%)	-	5.42	2.47	0.97	0.95	0.97
7	FRIABILITY (%)	-	0.964	0.521	0.266	0.197	0.160
8	DRUG CONTENT (%)	-	97.65	97.86	96.59	99.45	101.80

TABLE 21: **Sieve Analysis for Core Pellets**

S.NO	SIEVE NO	PERCENTAGE OF SAMPLE RETAINED IN EACH SIEVE					
		F1	F2	F3	F4	F5	F6
1.	18	-	8.4	7.9	2.5	1.9	1.4
2.	20	-	3.4	2.8	1.4	1.0	0.97
3.	24	-	88.2	89.3	96.1	97.1	98.03
4.	Pan	-	-	-	-	-	-

8.2.1. Evaluation of Diclofenac Sodium Capsules Filled With Core Pellets

The pellets formulated from trial F2, F3, F4, F5 and F6 were filled into "1" size capsules in semi automatic machine. The weight variation tests were performed and the value lies between 401.3 ± 2.43 to 406.2 ± 2.23. The values are mentioned in table no: 22 and observed to be within I.P Limit ± 5%.

Assay was performed for randomly selected 10 capsules from each trial. The values range from 97.59-101.88. The results shows all the capsules of each trials containing drug were within the limit (90 - 110%) as per I.P.

To ensure the consistency of dosage units, each unit should have drug content within a narrow range around the label claim. Therefore test for content uniformity is performed. .Ten capsules randomly selected from each trial (F2-F6), Contents were removed and drug content present in each capsule is calculated. The average of ten capsules is calculated and values are given in table no: 22 the results show all the capsules were within the limit. (90-110%) as per I.P.

The evaluation was continued with *in-vitro* dissolution studies. Filled capsules were used for same.

The formulation F2 with 24% MCC and 2% PVP K30 released 78.23% at 15 minutes,84.25% at 30 minutes and 94.36% after 45 minutes .Formulation F3 with 28% MCC and 3% binder concentration showed 98.20% of drug release after 45 minutes.

The dissolution data for formulation F4 with 32% of MCC and 4% PVP K30 demonstrates 45.67% at 15 minutes, 63.45% at 30 minutes and 82.39% after 45 minutes. The release profile for formulation F5 was not satisfactory and it does not complies with IP limit Therefore formulation F5 was tried by reducing the concentration of MCC to 30% and PVPK30 to 3%.The drug is released 99.83% after 45 minutes. The results were confirmed by taking reproducibility batch F6 with 30% MCC and 3% binder concentration. The results showed 99.21% at 15 minutes, 103.60% at 30 minutes and 104.30% after 45 minutes.

The dissolution data for formulation F2-F6 were given in the table no: 23 and the values were plotted in graph: 3

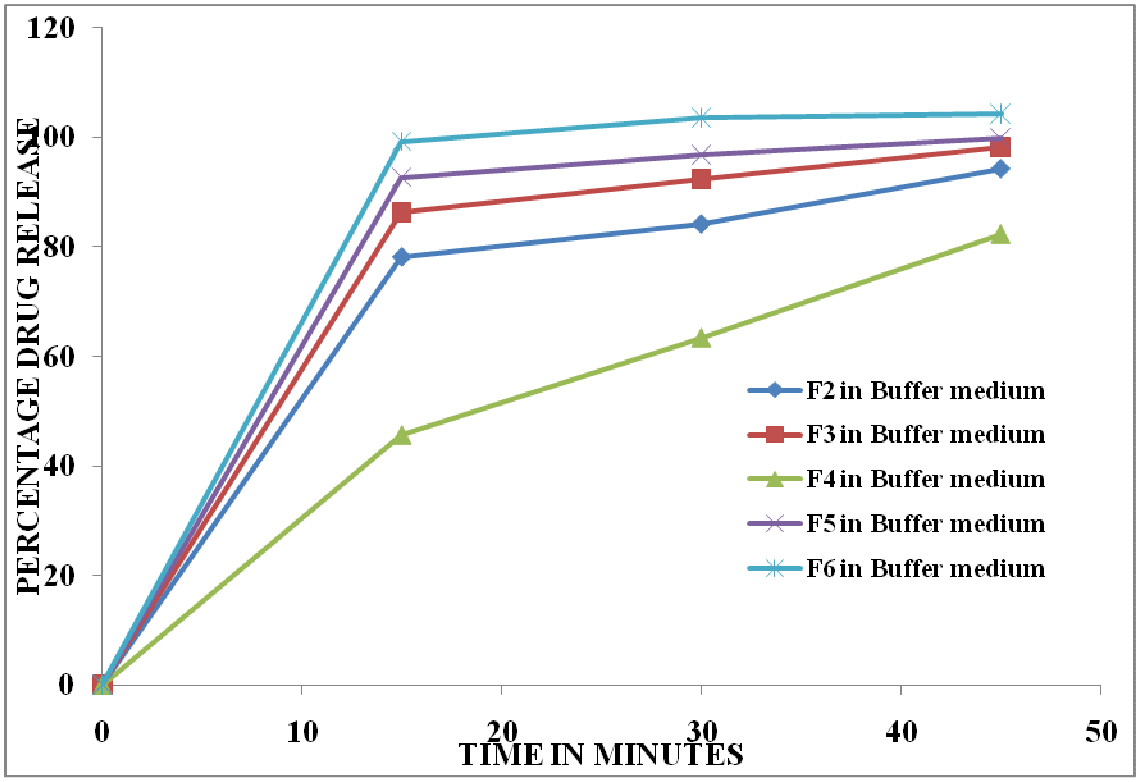
TABLE 22**: Evaluation of Diclofenac Sodium Capsules (F1-F6)**

S. No	Formulations	Weight variation in (mg) ± S.D	Drug content(%)	Cumulative % Content uniformity of 10 capsules
1.	F1	-	-	-
2.	F2	401.3 ± 2.43	99.84	98.73
3.	F3	405.6 ± 3.04	97.59	97.45
4.	F4	405.3 ± 2.40	99.38	101.67
5.	F5	406.0 ± 2.18	99.40	99.05
6.	F6	406.2 ± 2.23	101.88	99.38

TABLE 23: ***In-Vitro*** **Release Study of Core Pellets (F1-F6)**

S.No	Stage	Time In Minutes	Percentage Drug Release Of Core Pellets					
			F1	F2	F3	F4	F5	F6
1.	BUFFER STAGE	15	-	86.21	90.37	39.26	99.20	98.23
2.		30	-	92.30	94.81	45.24	102.60	101.40
3.		45	-	98.20	99.83	76.42	104.30	103.64

GRAPH: 3 ***In-Vitro*** **Release Study of Core Pellets (F1-F6)**



8.3. Evaluation of Enteric Coated Pellets (C1-C8)

Formulation C1- C8 was designed by enteric coating the core pellets of optimized formulation different enteric coating polymers such as Kollicoat MAE 100P and Eudragit L 100. The micromeritic properties such as bulk density, tapped density, angle of repose, hausner's ratio, and Carr's index were studied. The overall results were tabulated in table no: 24

The angle of repose for the formulations C1-C8 ranges from 25.23^{o} - 24.22^{o} which depicts excellent flow character. Bulk density ranges from 0.714 gm/ml-0.820gm/ml. Tapped density for the enteric coated formulations C1-C8 lies between 0.732gm/ml-0.859 gm/ml.

Hausner's ratio for enteric coated pellet formulations (C1-C8) ranges from 1.02 gm/ml-1.10 m/ml .The values shows the property of excellent flow character. Percentage of Carr's index for the formulations C1-C8 was found to be 2.40, 3.05, 2.67, 3.88, 8.98,

4.31, 9.17 and 5.00% respectively. These values demonstrates the excellent flow character of formulations C1-C8

TABLE 24: **Evaluation of Enteric Coated Pellets (C1-C8)**

FORMULATION	C1	C2	C3	C4	C5	C6	C7	C8
ANGLE OF REPOSE (degrees)	25.23	26.62	25.95	28.94	26.10	27.26	25.95	24.22
BULK DENSITY(gm/ml)	0.714	0.746	0.764	0.792	0.816	0.734	0.812	0.820
TAPPED DENSITY(gm/ml)	0.732	0.792	0.785	0.824	0.857	0.778	0.894	0.859
CARR'S INDEX (%)	2.40	3.05	2.67	3.88	8.98	4.31	9.17	5.00
HAUSNER'S RATIO	1.02	1.06	1.05	1.04	1.01	1.10	1.10	1.06
LOSS ON DRYING (%)	0.79	0.85	0.94	0.97	0.96	0.90	0.85	0.97
FRIABILITY (%)	0.214	0.175	0.326	0.563	0.459	0.523	0.143	0.965
DRUG CONTENT (%)	101.05	97.65	95.76	101.67	99.32	99.45	101.84	107.71

Sieve analysis was performed in a sieve shaker with a set of sieves (18, 20, and 24) to determine the particle size and its frequency of distribution. Percentage of sample retained in each sieve was calculated. As the pellets are enteric coated the size of the

pellets is slightly greater than the core pellets. This is evidently shown from the results tabulated in table no: 25 the percentage of sample retained in each sieve (18, 20, and 24) are greater than core pellets. The pellets are smooth and uniform. Maximum percentage of sample retained in sieve no: 24. From the results the size of the pellets lies between 1.40-1.00 mm.

The friability for coated pellets were checked and it ranges from 0.214-0.965% w/w and the values depicts friability is within IP limit which is not more than 1% w/w, indicating the sufficient mechanical integrity and strength of prepared pellets.

Loss on drying for the formulations C1-C8 ranges from 0.79-0.97 % .The values were within 1% and complies within IP limit.

Drug content of formulations C1-C8 was found to lie between 95.76%-107.71%.the results shows all formulation containing drugs were within the limit (90-110%) as per IP.

TABLE 25: **Sieve Analysis for Enteric Coated Pellets**

S.NO	SIEVE NO	PERCENTAGE OF SAMPLE RETAINED IN EACH SIEVE (%)							
		C1	C2	C3	C4	C5	C6	C7	C8
1.	18	10.9	11.5	11.8	10.5	12.6	13.7	12.4	14.8
2.	20	23.9	30.4	30.0	31.9	47.8	49.3	48.2	50.6
3.	24	65.2	58.1	58.0	57.6	39.6	37.0	39.4	34.6
4.	Pan	-	-	-	-	-	-	-	-

8.3.1. Evaluation of Diclofenac Sodium Enteric Coated Capsules (C1-C8)

The enteric coated pellets were filled in “0” size capsules and checked for weight variation .The coating was done up to 15% of weight gain of total weight of core pellets. The average weight of each capsule ranges from 475.2± 1.17 – 478.3 ± 1.04. The

formulations C1-C8 was observed to be within I.P limit ± 5%. Their values are mentioned in table no: 26

Assay was performed for randomly selected 10 capsules from each trial. The values range from 98.29-101.04. The results shows all the capsules of each trials containing drug were within the limit (90 - 110%) as per I.P.

To ensure the consistency of dosage units, each unit should have drug content within a narrow range around the label claim. Therefore test for content uniformity is performed. .Ten capsules randomly selected from each trial (C1-C8), Contents were removed and drug content present in each capsule is calculated. The average of ten capsules is calculated and values are given in table no: 26 the results show all the capsules were within the limit. (90-110%) as per I.P.

The dissolution studies for the formulations C1-C8 was performed in capsules filled with enteric coated pellets.

8.3.2. In-Vitro Dissolution for Enteric Coated Capsules (C1-C8)

The dissolution study was carried out in USP Type II dissolution apparatus. The samples were subjected to acid medium (0.1N HCl) for two hours and continued with pH 6.8 phosphate buffer for 45 minutes. The samples were collected and checked for absorbance at 285 nm in UV-Spectrophotometer.

The results were interpreted by plotting the graph with cumulative percentage drug release versus time in minutes in graph no: 4

Formulation C1 enteric coated with 10% w/v of Kollicoat MAE 100P produced 64.17% of release in acid medium. So, the formulation C2 was coated with 2% ethyl cellulose as seal coat to the pellets and 10% of enteric coating was done in combination to the seal coated pellets with Kollicoat MAE 100P the result was obtained as 39.85% of drug released within 2 hours in acid medium. To further reduce the drug release in acid medium the concentration of enteric coating polymer alone was increased as 15% with Kollicoat MAE 100P alone in the formulation C3, 59.92% of drug released, the result was improved when compared with C1 but worse than C2, Hence formulation C4 was

tried with 2% of seal coat in combination with 15% of Kollicoat MAE100P, and the acquired result was 29.93% of Diclofenac sodium release. Above results shows that, formulation C4 had quiet good improvement in the retarding of Diclofenac sodium release in 2 hours of acid medium when compared with the other formulation from C1 to C3, Even though desired drug retard with Kollicoat MAE 100P was not achieved. So, the alternate enteric coating polymer Eudragit L100 was decided to apply in the further formulation.

Formulation C5 was coated with 10% of Eudragit L100 alone to the core pellets and the result was obtained as 24.65%. To retard the drug release more the formulation C6 was tried in the combination of 2% seal coat and 10% Eudragit L100 to the core pellets, the drug release was attained as 15.65%.To retard the drug release lesser than 10% the concentration of Eudragit L100 alone increased to 15% in the formulation C7 and sprayed to the core pellets, but the result was 11.63% which is not sufficient drug retard for the enteric coating dosage form. Hence, formulation C8 was tried with 2% seal coat and 15% Eudragit L100 and the Diclofenac sodium was released only 0.59% in the acid medium at 120^{th} minute.

From the above observation, formulation C1 to C6 does not complies with desired drug retard in the acid stage dissolution and the continuous buffer stage dissolution was not performed to it. Formulation C7 and C8 had a better drug retarding property so the process was carried to next continuous pH 6.8 phosphate buffer stage for 45 minutes. Formulation C7 shows 81.26% at 15^{th} minute, 94.12% of drug release at 30^{th} minute and 98.80% at 45^{th} minute. Formulation C8 shows 77.15%, 92.87% and 98.24% at 15, 30 and 45 minutes respectively.

When compared to C7, formulation C8 has shown negligible amount of Diclofenac sodium release in 0.1N HCl and almost maximum amount of drug releases in 6.8 Phosphate Buffer which is the desired and optimum for the formulation of Diclofenac sodium enteric coated pellet dosage form.

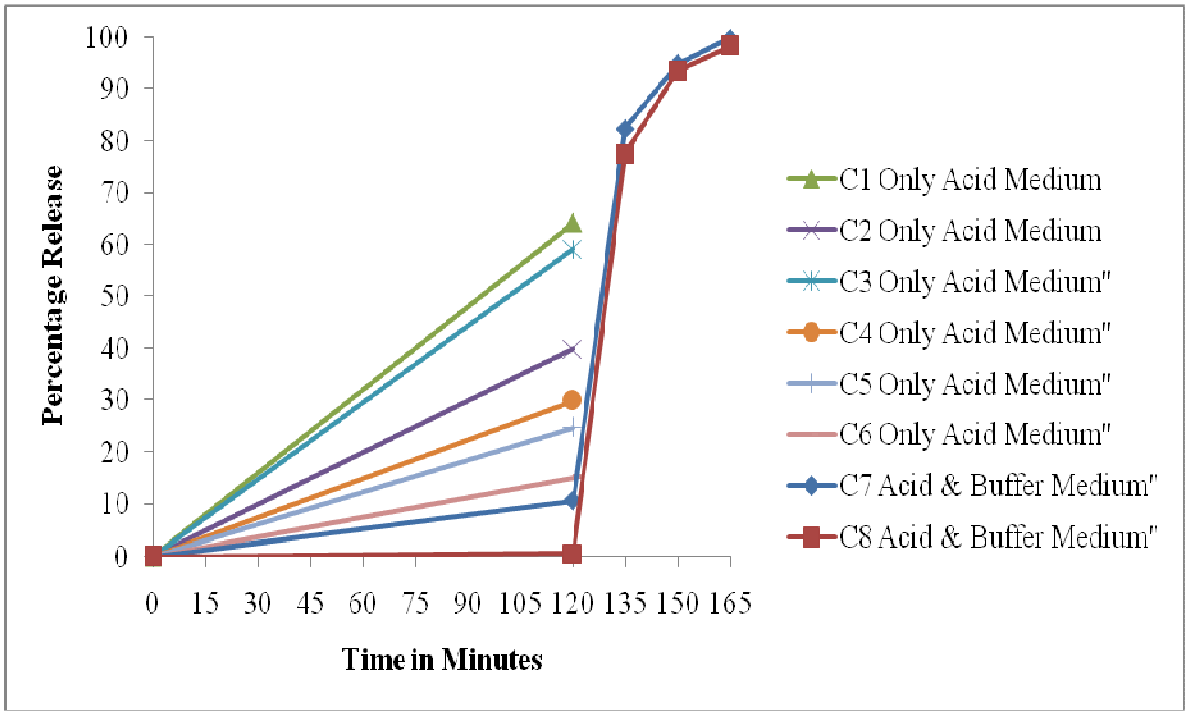
TABLE 26: **Evaluation of Diclofenac Sodium Enteric Coated Capsules (C1-C8)**

S.No	Formulations	Weight variation in (mg) ± S.D	Drug content (%)	Cumulative % Drug content of 10 capsules
1.	C1	478.3 ± 1.04	99.56	99.73
2.	C2	476.0 ± 1.62	99.90	98.00
3.	C3	476.6 ± 1.20	98.29	100.60
4.	C4	475.9 ±1.11	99.08	101.88
5.	C5	475.2 ± 1.17	99.00	99.67
6.	C6	477.1 ±1.08	100.58	99.21
7.	C7	476.4 ± 0.99	101.04	101.98
8.	C8	476.5 ± 0.91	98.77	101.39

TABLE 27: **In-Vitro Evaluation of Enteric Coated Pellet Formulations (C1-C8)**

S.NO	STAGE	TIME IN MINUTES	PERCENTAGE DRUG RELEASE OF ENTERIC COATED PELLETS							
			C1	C2	C3	C4	C5	C6	C7	C8
1.	ACID STAGE	120	64.17	39.85	59.92	29.93	24.65	15.65	11.63	0.59
2.	BUFFER STAGE	15	-	-	-	-	-	-	81.26	77.15
3.		30	-	-	-	-	-	-	94.12	92.87
4.		45	-	-	-	-	-	-	98.80	98.24

GRAPH: 4 **In-Vitro Release Study of Enteric Coated Pellets (C1-C8)**



8.4. Scanning Electron microscopy

The particle size of core pellets ranges from 725.11µm- 961.82µ mm and the particle size of enteric coated pellets range from 1.19µm – 1.31 mm. The particle size of core pellets seems to be increased after coating process. These results are evident from SEM Photographs given in figure 17 & 18

FIGURE 17: **Scanning Electron Microscope Pictures of Diclofenac Sodium core pellets**

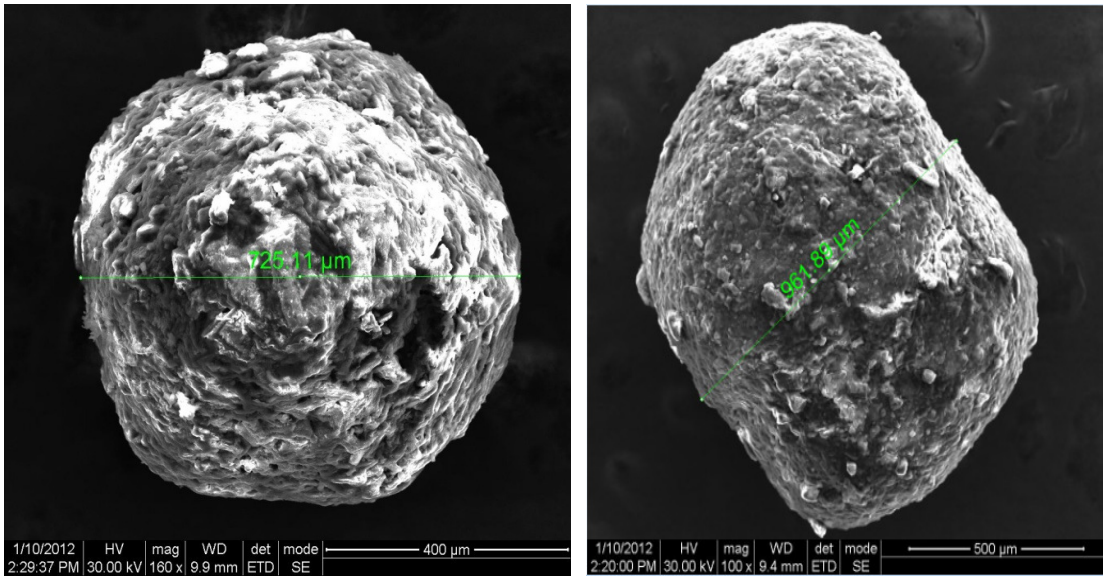
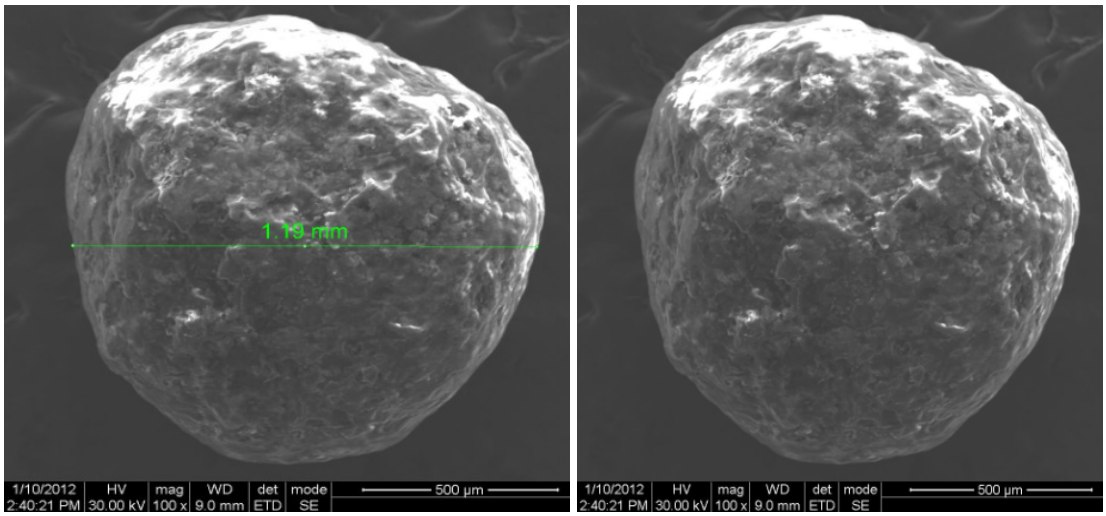


FIGURE 18: **Scanning Electron Microscope Pictures of Diclofenac Sodium Enteric coated pellets**



PHOTOGRAPHS OF DICLOFENAC SODIUM FILLED CAPSULES

A) CORE PELLETS FILLED IN CAPSULES

B) BLISTER PACKED ENTERIC COATED PELLETS FILLED IN CAPSULES

8.5. Stability studies of optimized pellet formulation (C8)

Stability studies were conducted for the capsules with optimized pellet formulation (C8).The stability study was performed at 40°C ± 2° C / 75% RH for a specific time period. The capsules were analyzed for weight variation, friability, drug content, and invitro dissolution after a period of 30 and 60 days. The results obtained are shown in table no: 29 the formulation showed acceptable limit in weight variation, hardness, friability, thickness, drug content, and invitro dissolution. The overall results showed that the formulation is stable for a period of 60 days. Cumulative percentage of drug release was plotted in graph no: 5

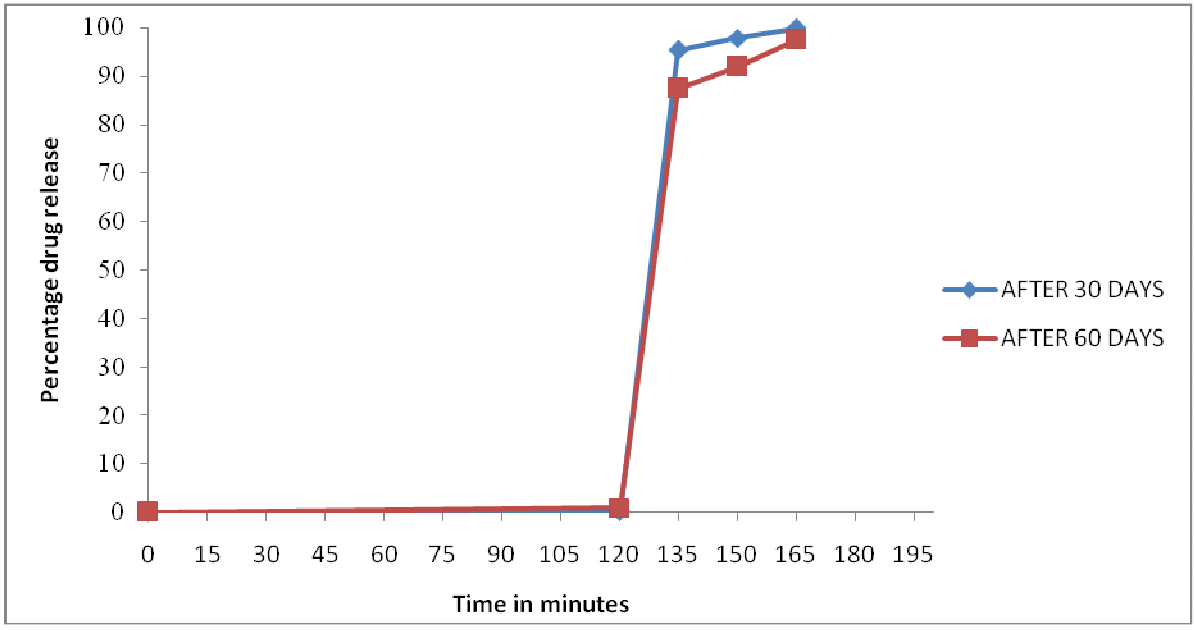
TABLE 28: **Accelerated Stability Data of Capsule with Optimized Pellet Formulation (Storage Condition: 40°C/75%Rh)**

S.NO	TESTS	FIRST MONTH	SECOND MONTH
		OPTIMIZED PELLET FORMULATION	**OPTIMIZED PELLET FORMULATION**
1.	**Capsule Description**	Orange/clear "1"size capsules.	Orange/clear "1"size capsules.
	Pellet Description	Orange colored spherical shaped enteric coated pellets.	Orange colored spherical shaped enteric coated pellets.
2.	**Average weight**	476.4±1.04	475.2±0.99
3.	**Weight variation**	0.01% within the limit	0.03% within the limit
4.	**Friability**	0.54% within the limit	0.65% within the limit
5.	**Drug content**	99.69%	97.39%

Table 29: **In-Vitro Dissolution of Formulation C8**

Invitro dissolution after 30 days at 40°c / 75%rh			Invitro dissolution after 60 days at 40°c / 75%rh		
Dissolution medium	**Time in minutes**	**Cumulative percentage drug release**	**Dissolution medium**	**Time in minutes**	**Cumulative percentage drug release (%)**
0.1 N HCl	120	0.68	**0.1N HCl**	120	0.95
Phosphate Buffer pH 6.8	15	95.35	**Phosphate Buffer pH 6.8**	15	87.45
	30	97.84		30	91.87
	45	99.84		45	97.45

GRAPH: 5 **After 30 &60 Days in Accelerated Stability Studies**



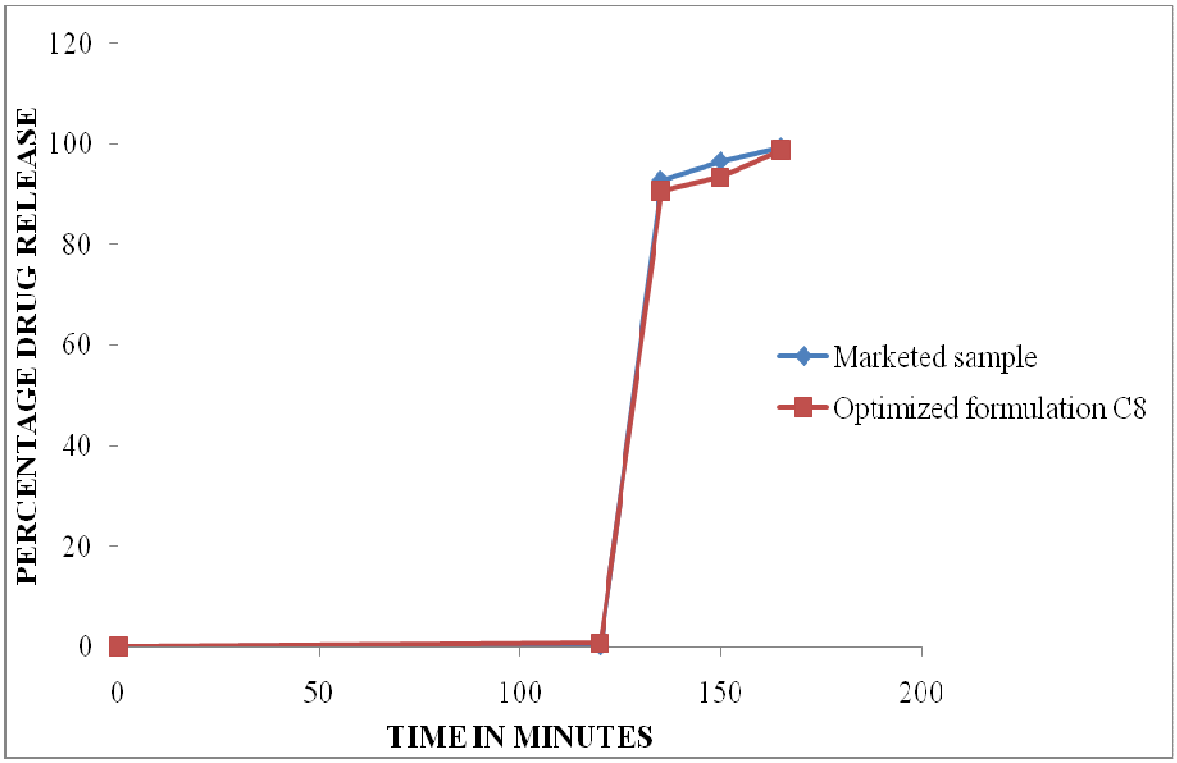
8.6. Comparison of Optimized Pellet Formulation C8 with Marketed Product:

The optimized formulation C8 was compared with marketed sample. The invitro dissolution of marketed sample was depicted in the table no: 30. Comparative invitro dissolution between optimized formulation C8 and marketed sample was plotted in graph no: 6. Marketed sample showed a cumulative release of 0.25% in acid medium and 99.28% of Diclofenac sodium in buffer medium. Formulation C8 showed 0.69% of drug release in 0.1N HCl and 98.90% of drug in Phosphate Buffer pH 6.8. The overall result indicated formulation C8 is comparatively similar with marketed sample.

Table no: 30 **Comparative in-vitro dissolution of Optimized enteric coated pellet Formulation C8 Vs Marketed formulation**:

S.no	Stage	Time in minutes	Percentage drug release (%)	
			Optimized formulation(C8)	Marketed formulation
1.	**Acid stage (0.1N Hcl)**	120	0.69	0.27
2.	**Buffer stage (Phosphate Buffer Ph 6.8)**	15	90.65	92.74
3.		30	93.42	96.51
4.		45	98.90	99.28

GRAPH NO: 6 **Comparative in-vitro dissolution of marketed sample Vs optimized pellet formulation (C8)**



9.SUMMARY AND CONCLUSION

A present work attempts have been made to fabricate Diclofenac sodium enteric coated pellet formulation by Extrusion-Marumerisation technique for the treatment of Osteo – Arthritis and Rheumatoid Arthritis.

Diclofenac sodium has been reported with GI Bleeding ,Ulceration and Perforation which can be fatal. So Diclofenac sodium was enteric coated with two different enteric coating polymers namely Kollicoat MAE 100P and Eudragit L 100 to retard the release in stomach and made available in intestine.

The core pellets were fabricated using Micro crystalline cellulose, Lactose monohydrate and Poly vinyl pyrolidone K30. Six trials was performed with different concentration of MCC,Lactose and PVP K30. Micrmeritic properties and dissolution profile were studied and among six trials F6 showed best results and considered to be optimized formulation.

The physical compatibility evaluation was performed in FTIR and DSC. The study complies that the drug, polymer and other excipients were physically compatible with each other.

The optimized formulation was taken for enteric coating. Eight trials were performed. C1-C4 is coated with 10% and 15% of Kollicoat MAE 100P using non–aqueous solvents.C2 and C4 is seal coated with 2% ethyl cellulose. Pellets were filled in “0” capsules and evaluated. The results failed the specifications of enteric coating. So, in further trials C5-C8 polymer was changed to Eudragit L 100.C5-C8 is coated with 10% and 15% polymer.C6 and C8 is seal coated with 2% ethyl cellulose and finally coated with Eudragit L 100. The final formulation C8 shows only 0.59% of drug release in acid media and 99..84% in buffer media. Finally diclofenac sodium enteric coated pellets with good retarding property in acid media and good release profile in buffer media is fabricated and evaluated. SEM analysis were performed for determining the particle size and surface characteristics of fabricated pellets. The coated pellets were greater in size when compared to Uncoated pellets.

CONCLUSION

The present research work was carried out to prepare enteric coating pellet dosage form using Diclofenac sodium for the effective therapy in Osteoarthritis and Rheumatoid Arthritis.

Diclofenac sodium pellets were fabricated and enteric coated with two different polymers namely Eudragit L 100 and Kollicoat MAE 100P with different ratios.

Diclofenac sodium enteric coated pellet formulation C8 with 2% seal coat of ethyl cellulose and 15% of Eudragit L l00 showed 0.59% in acid medium (0.1N HCL) and 98.24% in Buffer medium (Phosphate buffer PH 6.8).

From this research work it is evident that the formulated pellet formulation has ability to retard the release of diclofenac sodium in stomach and made available in intestine, which shows similar drug release profile when compared to the marketed formulation.

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